Exhibit D

UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

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KATRINA DAWN COPLEY, Plaintiff,	:	CIVIL ACTION NO. 3:14-cv-00406
vs.	:	
BAYER HEALTHCARE PHARMACEUTICALS, INC., BAYER PHARMA AG, and BAYER OY, Defendants.	:	

ADDITIONAL CAPTIONS LISTED ON NEXT PAGE

- - -

Wednesday, May 4, 2016

- - -

Videotaped deposition of DAVID WILLIAM FEIGAL, JR., M.D., M.P.H., held at COVINGTON & BURLING, L.L.P., 2029 Century Park East, Suite 3100, Los Angeles, California, commencing at approximately 9:06 a.m., before Rosemary Locklear, a Registered Professional Reporter, Certified Realtime Reporter and California CSR (#13969).

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UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ALABAMA

SHAMEKA M. BRIDGES, AND PETERSON BRIDGES, Plaintiffs, : CASE NO. 2:14-cv-00036-WMA
vs.
BAYER HEALTHCARE PHARMACEUTICALS, INC., BAYER PHARMA AG, and BAYER OY, Defendants.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF INDIANA
HAMMOND DIVISION

KATHLEEN CHEEK and BILLY CHEEK, Plaintiffs, : CASE NO. 2:15-cv-00020
vs.
BAYER HEALTHCARE PHARMACEUTICALS, INC., et al., Defendants.

UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF MISSOURI
WESTERN DIVISION

SARAH D. HOOVER Plaintiff, : CIVIL ACTION NO. 3:14-cv-05090-SRB
vs.
BAYER HEALTHCARE PHARMACEUTICALS INC., BAYER PHARMA AG, and BAYER OY, Defendants.

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ALABAMA

SHENIKA J. HOUSTON, Plaintiff, : CASE NO. 2:14-cv-00035-WMA
vs.
BAYER HEALTHCARE PHARMACEUTICALS INC., et al.,: Defendants.

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF VIRGINIA

EMILY C. KELLINGTON Plaintiff, : CASE NO. 5:14-cv-00002-MFU
vs.
BAYER HEALTHCARE PHARMACEUTICALS INC., Defendant.

APPEARANCES:

JONES WARD, P.L.C.
BY: LAWRENCE L. JONES, II, ESQUIRE
larry@jonesward.com
BY: CHRISTINA NATALE, ESQUIRE
christina@jonesward.com
Marion E. Taylor Building
312 South Fourth Street, 6th Floor
Louisville, Kentucky 40202
(502) 882-6000
Appearing on behalf of the Plaintiffs

COVINGTON & BURLING, L.L.P.
BY: PAUL W. SCHMIDT, ESQUIRE
pschmidt@cov.com
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
(202) 662-6000
Appearing on behalf of the Defendants

ALSO PRESENT:

RYAN WONG, Video Operator

I N D E X

EXHIBIT INDEX

EXHIBIT INDEX (Continued)

(Exhibits retained by the court reporter and attached to transcript.)

VIDEO OPERATOR: We are now on the record.

My name is Ryan Wong. I am a videographer for Golkow Technologies. Today's date is April 4th, 2016, and the time is 9:06 a.m.

MR. JONES: May the 4th.

MS. NATALE: May the 4th.

VIDEO OPERATOR: Oh, May the 4th. I'm sorry.

This video deposition is being held in Los Angeles, California, in the matter of Katrina Copley versus Bayer HealthCare and others, for the United States District Court, Middle District of Tennessee.

The deponent is Dr. David Feigal.

Counsel, please identify yourselves for the record.

MR. JONES: Larry Jones for the plaintiffs.

MS. NATALE: Christina Natale for the plaintiffs.

MR. SCHMIDT: Paul Schmidt for Bayer.

And we cross-noticed this in a few other cases so if you don't have the caption, I can get them to you at a break.

VIDEO OPERATOR: The court reporter is Mary (sic) Locklear, and will now swear in the witness.

DAVID WILLIAM FEIGAL, JR., M.D., M.P.H., having been duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. JONES:

Q. Good morning, sir. My name is Larry Jones. We met just a couple of moments ago. I represent the plaintiffs in this case.

And my phone is dinging, and that's probably a good lesson to everyone to turn their phones off.

Can you please state your full name for the record.

A. Yes. My name is David William Feigal, Junior.

Q. Okay. And, Doctor, you're a Medical Doctor; correct?

A. That's correct.

Q. And, Dr. Feigal, where do you currently reside?

A. I reside in Santa Rosa Valley, California.

Q. Okay. And do you intend to appear live to testify at the trial in these cases?

A. If asked, yes, I would.

(Exhibit Feigal-1 was marked for identification.)

BY MR. JONES:

Q. Dr. Feigal, I'm going to hand you a document that we're marking as Plaintiff's Exhibit 1 --

A. Yes.

Q. -- which I will represent to you is the

Deposition Notice served in this case.
Have you seen this document before?
A. Yes, I have.
Q. Okay. And the Deposition Notice asks for certain documents --
MR. JONES: I don't have an extra copy.
MS. NATALE: Do you need one?
BY MR. JONES:
Q. How many document requests are there on there? I don't have a copy.
A. Oh. 23.
Q. Okay. And did you -- have you seen this before?
A. Yes.
Q. And did you engage in efforts to try to locate the documents listed here in the Deposition Notice?
A. Yes, I did.
Q. And tell me what kind of efforts you engaged in to locate the documents listed in the Deposition Notice.
A. I went down through the list to see which of these documents I had. Some of them aren't things that I have or ever had, some of them -- and I had discussions with Mr. Schmidt about which of these I was to produce and so then I went through my files and pulled the documents that I could and I've brought them with me today.

Q. Okay. And do you have those documents with you here today?
A. Yes, I do.
Q. And can I have them?
A. Sure.
This is just a copy of my report.
Q. Okay.
A. But what I'm providing for you are the documents, each of them have a yellow sticky on them which indicates which number of the Document Request it is.
Q. Okay.
A. And then I've also brought for you an updated copy of my prior testimony since.
Q. Okay.
A. Since we've submitted that initially, I've done two depositions, and they're reflected on that new list.
Q. Okay. So it looks like you've provided an updated CV in response to Items 1 and 2 on the document list; is that correct?
A. That's correct. I believe it's the same CV that I submitted before, but I brought one for your convenience.
Q. Okay. And then the next thing that it looks like you've produced -- and I appreciate the sticky

notes -- is you responded to Request Number 23 with a copy of several invoices; is that correct?
A. Yes. Those are actually all of the invoices over time that relate to Mirena, not just this case but other cases before then.
Q. When you say "other cases before then," what are you talking about?
A. I was originally retained to prepare a report on Mirena and issues relating to uterine perforation, and so most of the invoices actually reflect that. The work -- the invoices for IIH began in February of this year. There's two copies there, by the way.
Q. Oh, okay. Great.
Is there two copies of everything?
A. Except for the CV.
Q. Okay.
MR. JONES: I'm going to mark a copy of these invoices as Deposition Exhibit Number 2.
(Exhibit Feigal-2 was marked for identification.)
BY MR. JONES:
Q. And is Exhibit Number 2, is that a true and accurate copy of what you just described regarding your invoices?
A. Yes, it is.

Q. Okay. And then the next item that you've provided is -- has a sticky note that says "25" on it so that's -- you're responding to Document Request Number 25; is that correct?
A. Actually, it's probably 22. Because there is no 25.
Q. Yeah, that's what I was going to say. It says "25" on it --
A. Yeah.
Q. -- on the sticky, but there's -- it doesn't -- this doesn't go up to 25.
A. It's 22.
Q. Okay.
A. Yeah. And -- yeah.
Q. And that Item 22 says, all consulting contracts or retention letters concerning the witness's involvement in the Mirena litigations.
A. Yes, that's correct.
Q. So that's --
A. That's the original -- that's the original retainer letter and a modification letter where my rates changed.
Q. Okay.
MR. JONES: Let's mark that as Deposition Exhibit Number 3.

(Exhibit Feigal-3 was marked for identification.)
MR. JONES: Paul, did you want this back?
MR. SCHMIDT: Yes.
BY MR. JONES:
Q. And then there is a -- one copy of an updated prior testimony list?
A. Yes.
Q. Is that correct?
A. That's correct. Yeah. I already gave a copy to Mr. Schmidt.
Q. Now, can you -- I've received a previous list of your testimony.
Can you help me understand, was this merely your attempt to update to date or were there additions within the body of the other?
A. No, there's no additions within the body. There may have been one that dropped off because it's now before the four-year time period, but there's two additions on the last page.
So I think there's one deletion, the first line on the old report has been deleted because now it's longer than four years ago, and then there's two additions for two depositions that are done recently.
Q. And the list of your prior testimony is three,

four, five, six pages for the last four years; is that correct?
A. That's correct.
Q. Okay. So you've given sworn testimony before?
A. I have.
Q. How many times in your life have you given a deposition?
A. Well, I've probably -- I did my first deposition, actually, as a fact witness for the Government in about 1995 but then not again until I began work as an expert.
I would say that there are probably, you know, an additional three or four trial, at-trial, testimonies before the ones on that list and there's probably an additional 10 or 15 depositions.
Q. Okay. So let's -- depositions in the last four years, we have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12?
MR. SCHMIDT: Do you have a copy that he could follow along with?
MR. JONES: He only gave me one copy.
THE WITNESS: I gave you one and I gave you one. Why don't I look at the one I gave you.
MR. JONES: Okay.
BY MR. JONES:
Q. Let me -- depositions, 1, 2, 3, 4, 5, 6, 7, 8,

9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, plus you say probably another 10 or 15 before this period; is that correct?
A. Yes; going all the way back to 1995. Yes.
Q. Okay. So 46 to 51 depositions.
And you said going all the way back to 1995, but I understood you a second ago to say that after you testified for the Government as a fact witness in '95, you hadn't testified at a deposition again until you started your consulting work; is that correct?
A. That's correct. The next deposition that I had was probably approximately in 2005.
Q. Okay. So since 2005, would it be fair to say that you've given between 46 and 51 depositions?
A. Yes.
Q. And that was as a paid litigation consultant?
A. Yes.
Q. And then let's look at -- you have a list of trial or arbitration testimony in the last four years. We have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20. 20.
So 20 instances of trial or arbitration testimony in the last four years?
A. That's correct.

Q. And how many did you say it would have been before the four-year period?
A. I don't recall what I said before. Probably four or five.
Q. Okay.
A. And I would point out that in the last -- in this list, half of them all relate to one matter, the cases involving Takeda Pharmaceuticals. So there were ten trials all on the same matter.
Q. But you were paid in those cases to -- you were paid for your time giving the testimony in those cases; correct?
A. Oh, yes.
Q. And you represent that you were an expert for Takeda in those cases?
A. Yes, I was retained by attorneys for Takeda. Yes.
Q. And those were involving Actos; right?
A. That's correct.
Q. And what was the claimed injury in Actos?
A. Bladder cancer.
Q. And were you testifying as a regulatory expert in those cases?
A. Yes. Also, to an extent, as an epidemiologist. But epidemiology is one of the tools of safety

surveillance, and I was providing testimony about post-market surveillance, regulatory, and the epidemiology that supported the labeling changes.
Q. Did you give testimony in those Actos cases that Takeda had adequately warned of the risk of bladder cancer in their product label?
A. Yes. Generally speaking, yes, that was the testimony that I offered.
Q. And did you give testimony in the Actos cases that Takeda's interactions with the FDA were appropriate?
A. With respect to the safety surveillance, yes, and the labeling updates and the submission of required documents, yes, I did.
Q. And those are similar to the opinions that you're giving in this case as well; correct?
A. At a very high level. But the facts are -- you know, the circumstances and the facts are very different.
Q. Sure. Okay. And you say that you were contacted to testify in the -- we'll call these -- the Mirena MDL, when I refer to that, is it fair to assume that those are the migration/perforation cases?
A. You can refer to them that way, yes.
Q. Okay. Is that a fair differentiation? I'm

trying to differentiate between these cases.
I'd like to call those the MDL or the migration/perforation cases and these the pseudotumor cerebri cases.
A. Sure, that's fine.
Q. Okay. And did I understand you to say that you were first contacted to testify in the pseudotumor cerebri cases in February of 2016?
A. '13. Oh, pseudotumor cerebri, that's '16, yes. February of '16.
Q. Okay. I do see that you first billed for the migration/perforation cases in February 2013. So are we sure that it was February on --
A. Yes.
Q. -- both?
A. Yes.
Q. Okay.
A. Yes.
Q. And who contacted you to discuss your potential expert retention in the pseudotumor cerebri cases in February of 2016?
A. Mr. Schmidt and his colleagues.
Q. Mr. Schmidt and his colleagues?
A. Yes.
Q. Okay. It wasn't anybody from Shook Hardy Bacon?

A. Not that I recall. I think with these cases I primarily interacted with the attorneys from Covington & Burling.
Q. Okay.
MR. SCHMIDT: And, Larry, I apologize. We also had a supplemental reliance list, if you wanted to review that at some point.
MR. JONES: Yes. Of course. Thanks.
MR. SCHMIDT: A few copies.
BY MR. JONES:
Q. Sorry for the lack of questions. I'm just going through --
A. No. No. That's quite all right.
Q. -- the documents that you gave me.
A. That's quite all right.
Q. The document that has a sticky note on it, 22, it did say "25" but we figured out it was 22, this appears to be a consulting agreement between your company, NDA Partners, L.L.C.?
Is that your company?
A. Yes, that's correct.
Q. Are you a partner in that company?
A. I am.
Q. A full equity partner?
A. Yes. There's 11 of us, yes.

Q. Okay.
A. I'm one of 11.
Q. Does your wife, does she work there?
A. She is. And she's now an equity partner as well.
Q. She is an equity partner?
A. Yes.
Q. Okay. I just wondered if -- I saw her bio and I thought, I wonder if they're related.
A. People ask me if we're related, and I usually say, yes, for the last 35 years.
Q. Yeah. They tell you you out kicked your coverage? Okay.
So I'm looking at a January 14th, 2013, letter from Hunter Ahern, partner at Shook, Hardy & Bacon, to Earle Martin --
A. Yeah.
Q. -- Earle Martin, partner and general manager, NDA Partners, L.L.C.
Is that a document that you produced to me?
A. Yes, it is.
Q. And January 14th, 2013, is this when you were retained for the migration/perforation cases?
A. Yes, it is.
Q. Okay. And it says that, we understand that you

have assigned David W. Feigal, M.D., M.P.H., to this project.

Who was the point of contact initially on this particular project? Was it Mr. Martin or was it you?

A. It was me.

Q. Okay.

A. And then to get an agreement between the attorney's firm and our group and to set up the billing arrangements, I turn that over to Mr. Martin and his staff.

Q. Okay. And it says, this will confirm that Bayer has authorized us to retain you as expert consultants in this matter at your customary fee of $500 per hour.

So that was your rate in 2013?

A. That's correct.

MR. JONES: Okay. Let's mark this as Deposition Exhibit 4 or 3? Four. Okay.

BY MR. JONES:

Q. Is that a --

MR. SCHMIDT: I'm sorry. What was 3? I thought that was 3.

THE WITNESS: No. Three was the -- oh, I've already got it marked as 3. I've got both copies.

MR. SCHMIDT: You marked the same one twice as two different numbers.

MR. JONES: Oh, I did?

Okay. So what do we have going on here?

THE WITNESS: Three and 4 are both the same.

MR. SCHMIDT: I think 3 and 4 are the same document.

MR. JONES: Oh. Oh, I gave you my copy. I'm sorry.

THE WITNESS: Yeah.

MR. JONES: So that's not Exhibit 4. Let's strike that.

Here's your sticker back.

BY MR. JONES:

Q. And is that a true and accurate copy of the retention letter, the initial retention letter, for your consulting arrangement with Shook Hardy Bacon and Bayer back in January 2013?

A. Yes, it is.

Q. Then we'll -- I'm looking at a letter that you've produced to Hunter Ahern, it's addressed to Hunter Ahern, partner, Shook Hardy & Bacon, October 22nd, 2014, from Ellen Teplitzky, T-E-P-L-I-T-Z-K-Y?

A. Yes.

Q. Okay. And this appears to be advising Shook Hardy that your new rate is $600 per hour for consulting and $700 per hour for deposition or expert witness

testimony; is that correct?

A. You've read that correctly but, actually, I only charge 600, no matter what the work is, so whether it's deposition testimony or whatever.

I think some of my other partners in the group have a differential rate. But I don't charge for travel or for depositions. So it's a flat 600 for my time, no matter what I'm doing.

Q. Okay. The next sentence says, non-productive travel time will be charged at $300 per hour.

Did I read that correctly?

A. Yes.

Q. And do you charge non-productive travel time at $300 per hour?

A. I do not. Some of my partners do that.

Q. Do you charge non-productive travel time at $600 per hour?

A. No, I don't charge for my travel time, just out-of-pocket travel expenses.

Q. And I think you clarified this for me but, as we sit here today, your billable rate is $600 per hour; right?

A. That's correct.

Q. Okay.

A. Whether it's deposition or report writing or

research, it's $600 an hour.

Q. And how often does your company raise your rate?

A. That was the first time we did it after, I think, nine years, and it's -- it was sort of across the board for multiple partners. We had had the same rate for about nine, ten years and we raised it.

Q. And do you testify at or do you bill at $600 per hour for consulting and deposition or trial testimony? When you work on other matters currently, is your rate $600 per hour?

A. For legal consulting, yes, it's the same for all of my clients.

MR. JONES: And then let's just go on and mark that as Deposition Exhibit 4.

(Exhibit Feigal-4 was marked for identification.)

BY MR. JONES:

Q. Dr. Feigal, did I mark a copy of these invoices yet or did you give me two copies?

A. No. You did mark it. That was Exhibit 2.

MS. NATALE: That's 2.

MR. JONES: Okay. Let's go to Exhibit 2, then.

MR. SCHMIDT: May I see Exhibit 4, please, David?

THE WITNESS: Sure.

BY MR. JONES:
Q. So you were first contacted to consult in this case in February of 2016; correct?
A. Yes. It looks like that's when the work started. You noticed the letter was dated in January. So I was probably contacted in January, I suggested we get a retainer letter in place, and then I started reviewing documents in February of 2013.
Q. Right. I'm talking about in the --
A. Oh.
Q. -- PTC cases.
A. I'm sorry. Yes. That's February of this year, yes, 2016.
Q. And there is no separate letter of consulting or agreement for this case, is there?
A. No, there is not.
Q. And so let's go back.
It looks like you've provided two invoices that relate to this case.
A. Yes.
Q. One is dated 3/14/2016, service date 2/29/2016.
That's just -- the service date is just the billed date; right? That's the last day of the month?
A. That's right.
Q. Okay. And then you go over, consultant, David

Feigal, description, for professional services rendered February 1st, 2016, to February 29th, 2016; is that correct?
A. Yes.
Q. Okay. And it looks like you spent 8.5 hours working on this case in February of 2016; correct?
A. That's correct.
Q. And what did you do during those exactly 8.5 hours during the month of February 2016?
A. As I recall, it was sometime in the second half of the month we had an initial couple-hour meeting here at this building to discuss the background of the case.
Prior to that, they had sent me a small number of documents that I reviewed before that meeting. And so this just reflects the time to review that document and those meetings and any document review I did after the meeting.
Q. And how many documents -- how long did the -- did you meet with the Covington & Burling lawyers once or more than once?
A. It was just once.
Q. And how long did that meeting last?
A. As I recall, it was two hours.
Q. Okay. And so for the other 6.5 hours, how many documents did you review?

A. I don't recall exactly.
Actually, I have one more thing which I've brought you in response to your request, and it's my working document. So you can see the documents that have highlighting, and if you look in here, you'll see folders by the dates on which I received documents.
Q. Okay.
A. So except for one -- there's one folder that's just labeled "IIH."
Q. Okay.
A. But you can see from probably the dates the documents were created or saved the rough time frame.
So this isn't the sum total of all the documents I've ever had for Mirena but it's the ones I've had since I began working on pseudotumor cerebri.
Q. Okay. And is that thumb drive for us?
A. Yes.
Q. Okay.
A. Yeah, it's for you.
Q. During February of 2016, were you provided with plaintiffs' expert reports in this case?
A. I was, yes.
Q. Okay. And how many of those expert reports were you provided with?
A. I think at that initial time I was provided Dr.

Ross, Dr. Etminan, never quite sure how to say Dr. Frau --
Q. Fraunfelder.
A. -- Fraunfelder's deposition, and one other whose name I can't remember.
Q. And you said "deposition," but those were --
A. I mean they --
Q. -- just reports; correct?
A. No. These were reports. That's correct. I later have -- I later have -- at a later point in time, I have depositions from Dr. Ross and --
Q. Would it --
A. Yeah.
Q. What about Dr. Mazzeo's report; were you ever provided with Dr. Mazzeo's report?
A. I don't recall. There was -- there were additional reports. I just -- I don't recall.
Q. At what point did you determine that you could give an expert opinion in this case for Bayer?
A. We had a follow-up conversation by telephone, as I recall, sometime in early March and I provided my initial, preliminary observations and opinions about the issues, particularly those in Dr. Ross's and Dr. Etminan's reports, and they asked me if I would begin working on a report. And at that point I began working

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on a report that would be filed. And when I do that, I'm also willing to offer testimony, if requested, at a deposition or trial.

Q. Okay. And we have -- going to the last page, the next invoice, it's dated 4/26/2016, for professional services rendered March 1st, 2016, through March 31st, 2016.

Did I read that correctly?

A. Yes.

Q. Okay. And 41.5 hours, for a total of $24,900 for that month; is that correct?

A. That's correct.

Q. Okay. And when you add that to the $5,100 from the prior month, you are at exactly $30,000; is that right? Is my math right?

A. It looks like that's correct.

Q. What work did you do during your 41.5 hours during the month of March 2016?

A. Well, during March, I filed the report that we have today. And so the work would have involved writing the report, reviewing the documents that were necessary to write that report, there were also conversations with attorneys during this time about the report and about some of my opinions.

Q. And what date did you submit your final report?

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A. The date is on Page 52 of the report. March 24th.

Q. And between the two invoices, it looks like you spent exactly 50 hours.

Well, does any of this 41.5 hours include time spent after you submitted your report?

A. It may have, but I suspect most of that will be in the April invoice, which hasn't been prepared yet.

Q. Right. I mean, after March 24th did -- was there any billable time after March 24th --

A. In the March?

Q. -- between -- yes, in the March period.

A. I don't think there was -- I don't think there was very much, if any.

Q. Okay. So you spent exactly 50 hours meeting with lawyers from Covington & Burling, reviewing documents, reviewing the expert reports of Dr. Ross, Dr. Etminan, Dr. Fraunfelder, and writing your report; is that correct?

A. That's correct.

Q. And how many pages is your report?

A. It is 52 pages.

Q. So that's less than an hour per page; correct?

A. Well, not all 52 pages are new. The background section on my background is the same, much of the

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background information on the initial approval of Mirena had been previously written for other reports. So 50 hours was the time necessary to write the material specific to pseudotumor cerebri.

Q. And can you go to the portion of your report that says "References Cited"?

A. Yes.

Q. Are you there?

A. Yes.

Q. Okay. And looking at this, this has 82 references that were cited in your report; correct?

A. Yes, that's correct.

Q. Okay. And as part of this 50 hours, did you review every one of these 80 references?

A. Well, some of these are references to sections that had been previously written, but if they are new references about pseudotumor cerebri, yes, I did review them.

Q. And did you review them cover to cover?

A. Not all of them. Some of them are documents that only small parts of the documents are relevant to the reference in the -- reference in the text. Others are documents that establish different regulatory milestones such as, you know, typically, I'll reference approval documents and reviews. But these are all --

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these are the reports among the total number of documents that I had that I, you know, specifically referenced in my report.

Q. Okay. And so those are the ones that you specifically referenced in your report, those 82 citations; correct?

A. That's correct.

Q. Okay. And then I have a listing of David Feigal M.D., materials reviewed.

Is that in your report? Do you see that?

A. I don't think I have that. Was that Exhibit B? Oh, wait. Wait. I do. Yes. Yes. It's here.

Q. Do you have it?

A. Yeah.

Q. Okay.

A. Yes.

Q. And it says "Academic Literature"; right?

A. Yes.

Q. Okay. And we have, I'm going to count them in my head to save the court reporter.

Okay. I count 89 pieces of academic literature that you reviewed; correct?

A. Yeah. Well, these -- yes, these are the materials that I had available to me and I'm familiar with all of them. I've reviewed some of them in more

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detail than others.
Q. Okay. Well, it says "Materials Reviewed."
Did you review these 89 materials or not?
A. Yes.
Q. Okay. So that's 89 plus the 82 that you cite so that's 171. Then you have --
A. Well, I would just point out, there may be duplicates because what I asked the Covington to do is to actually provide me a list of all the documents that they had provided to me, and so some of these documents will be on the citation, they should -- most of them will also be on this list.
Q. So Covington provided this list? They typed it up?
A. Yes. Yes. This is the one part of the report that I asked them to produce. I ask them -- I ask clients when I'm working for them to keep track of what they've sent me and to give a list of that and then I provide that to you so you know everything that I've been sent. And the materials I'm sent I review.
Q. And Covington provided all of these documents on Pages 1 through 12 of the Materials Reviewed; is that correct?
A. Substantially. There are some things, for example, statute and regulations, I also give them my

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list of things that are on my list that they didn't provide and then they add that to their list to create the comprehensive list.
Q. And then statutes, let's look at "Statutes and Regulations" on Page 7.
A. Sure.
Q. Looks like you reviewed seven statutory or regulatory sections; is that correct?
A. Yes. All of these are Federal Register notices of proposed and final rules pertaining to labeling, and then the Code of Federal Regulation, those are the labeling regulations.
Q. Okay. And then you have "Labels and Other Materials Obtained from Drugs@FDA Or Other Public Sources."
Do you see that?
A. Yes, that's right.
When I'm working with a material that's, you know, on a case that's FDA reviewed, I go to the FDA databases and I download copies there of the labels that I need and if there's reviews or other documents on the FDA website. So I obtain those myself, although oftentimes the law firm will send me the same documents. But I pull those directly.
Q. Okay. And that's eight items; correct?

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A. Yes, that's right.
Q. Okay. And then "Deposition Testimony," you have "Deposition of Juliane Schoendorf"; is that correct?
A. That's correct.
Q. Okay. And did you review that entire deposition from cover to cover?
A. I don't recall if I did or not. Some -- sometimes I use the index to find key sections, so I just don't recall if I read the entire thing.
Q. Were you provided the entire deposition?
A. Yes, I was.
Q. Do you remember how many pages it was?
A. Several hundred pages, but I don't remember exactly.
Q. Then you have "Documents Received From Plaintiffs" and you have two items; is that correct?
A. Yes.
Q. Then you have "Documents From Bayer Productions," and I'm going to count those.
And I count 69 items. Does that sound correct?
A. Does, yes.
Q. Okay. And then we have "Expert Reports," and I see three reports and the reliance materials provided by Dr. Ross and Dr. Fraunfelder; is that correct?
A. Yes. And Dr. Etminan.

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Q. Yeah. But no reliance materials for Dr. Etminan?
A. That's correct.
Q. Okay. Then this morning I've been, just now I've been provided with supplemental materials reviewed, and it looks like this is 11 depositions that you reviewed; is that correct?
A. Well, as provided, yes.
Q. I'm sorry?
A. Yes, as provided. And I familiarized myself with those depositions.
Q. Did you review them from cover to cover?
A. No, I did not.
Q. And the supplemental materials reviewed lists depositions of Dr. Fraunfelder, Dr. Etminan, Dr. Ross, Antonio Costales, Nancy Konnerth, Suzette Thomas, Leo Plouffe, Herman Ellman, Brenda Marczi, Paul Korner, and Chuck Walsh.
You didn't review those before you prepared your report, did you?
A. That's correct. If they're on the supplementary list, those are materials that I've reviewed between the production of the report and our conversation today.
Q. And why didn't you review these depositions before you issued your report?

A. I'd have to look at the timing to see if they were -- some of them were available. Company depositions were available. They were simply materials that I had not yet reviewed, but after the report, in discussing the issues in the case, I asked for them or the company -- or the attorneys thought it was relevant and they sent them to me.
Q. Okay. I'm going to back off the 11 depositions that were not reviewed before your report and, according to my calculations, give or take, there were approximately 265 documents that you reviewed before preparing your report; is that correct?
A. That's correct.
Q. And you did that in 50 hours.
A. Yes, that's correct.
Some of them I reviewed closely, others were for looking things up and were as part of a complete set of documents, not all of which I needed to rely on for the report.
Q. Do any of the -- did any of the medical literature that you reviewed suggest a causal association between levonorgestrel and pseudotumor cerebri?
A. I think some of the literature, particularly around the Norplant, raised that hypothesis. Most of

the authors in their papers usually conclude that more research is needed.
Q. Did any of the Bayer internal materials that you reviewed suggest a causal association between levonorgestrel and pseudotumor cerebri?
A. No, I don't think they did.
Q. Did you cite all of the materials that may have suggested a causal association between levonorgestrel and PTC in your report that you tendered in this case?
A. I did not cite all of the documents that I relied on in my report. The report cites the more important documents and selected documents but there are also materials in the list of materials reviewed that I reviewed and am familiar with, but I didn't attempt to create an exhaustive list of all the citations to all the documents.
Q. Did you do your own literature search in this case to look for medical literature or materials that suggest, that may suggest or disprove a causal association between levonorgestrel and PTC?
A. Yes, I did.
Q. Okay. And how much time did you spend doing your own literature search?
A. I don't recall exactly. I used PubMed and a service which will pull the full-text articles of the

literature from a PubMed search when they're in the public domain. Typically, such a search on a topic like that would take me several hours.
Q. Okay. And in this case, did you spend more or less than ten hours doing a literature search to determine whether or not there was or was not a causal association between levonorgestrel and pseudotumor cerebri?
A. Less than on the literature search itself. And, of course, there was also literature, much of the same literature that I came across in the PubMed search, that was provided to me in the materials or was referenced by plaintiffs' experts or was discussed at various times in the history of the FDA interactions for these -- for the products that we're reviewing.
So in terms of review of the literature, it's actually probably a significant fraction of the time, but the actual PubMed search didn't take me very long, just a few hours. And I used it primarily to get oriented to what the information is out there, to identify articles that I don't seem to have that the law firm can track down copies and provide copies for me.
Q. And how much time did you spend reviewing the literature that comprised the results of your literature search?

A. Well, I think that blends into the, you know, the literature search articles that I identified plus the literature that's -- that is -- pardon me -- is part of the production in the case or other documents.
That review all together is probably -- I would, you know, just have to estimate. But probably about 30 percent of the time in terms of the document review is taking a look at the medical literature that decisions are being made about and what other medical literature is available at the same time and at later points in time.
Q. So 30 percent of 50 hours would be about 15 hours; is that correct?
A. Yes. Embedded in the process of the review, yes. I don't track it separately.
Q. Now, other than the articles cited in your report, did you find any other medical literature or materials in which the authors suggested a causal association between levonorgestrel and pseudotumor cerebri?
A. I can't think of any sitting here right now, aside from the literature and aside from discussions in company and FDA documents, no.
Q. You don't believe that there's a causal association between levonorgestrel and pseudotumor

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cerebri; correct?
A. I believe at the present time that is -- that that is correct.
Q. But you realize that there are medical researchers out there who have published articles that disagree with you; correct?
MR. SCHMIDT: Object to the characterization.
THE WITNESS: I would have to look at their statements to see actually if we disagree.
There are authors that discuss the hypothesis that levonorgestrel causes pseudotumor cerebri. Oftentimes, in their discussions they point out the limitations of the available evidence and call for more research and place caveats. So you have to kind of look at what they say. But there are many -- there are papers, as you know, that have looked at that hypothesis that there could be a relationship.
BY MR. JONES:
Q. Have you ever heard of a doctor named Deborah Friedman?
A. Yes.
Q. Okay. And do you know Deborah Friedman?
A. I have reviewed -- I reviewed materials I believe that she's -- she has written. I would have to see the materials to refresh my memory on who she is.

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Q. Have you ever met her?
A. No.
Q. Have you ever talked to her?
A. No.
Q. Did you know that Bayer had hired her as a consultant on pseudotumor cerebri?
A. I may have known that. I'm familiar with the name from my review. I just don't remember the context of how I know her.
Q. Were you aware that she has written in at least one article that levonorgestrel implants are a cause of pseudotumor cerebri?
MR. SCHMIDT: Object to characterization.
THE WITNESS: I don't recall that, but I'd be happy to look at the article if you'd like me to comment on it.
BY MR. JONES:
Q. When you were doing your medical literature research and review, did you find any materials that you thought were counter to your position that there is no evidence of a causal association between levonorgestrel and pseudotumor cerebri?
MR. SCHMIDT: Object to characterization.
THE WITNESS: Well, the evidence all comes from observational studies and epidemiology, and there are

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authors from time to time that discuss that hypothesis and discuss that data.
As I mentioned, they usually -- you know, I'm not sure I can tell from the articles what their thinking or what their belief is. They often state the evidence for the hypothesis and also in the same breath talk about the limitations and how more research is needed.
MR. JONES: Okay.
BY MR. JONES:
Q. Getting back to your References Cited, looks like you cite a lot of medical journal articles. Is that fair?
A. Yes.
Q. Okay. Looks like you cite the Federal Register a few times; is that correct?
A. Yes.
Q. Okay. And those are proposed rule discussions and regulations that govern product safety at FDA. Is that fair?
A. Yes, there's both proposed and final rules in those citations. I usually -- most of them pertain to standards for labeling.
Q. Then it looks like you cite Physicians' Desk Reference.

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That's the PDR is what we know it as; right?
A. Yes, that's correct.
Q. And just so the jury knows, that's this big, thick book of labeling for products that doctors can refer to; right?
A. Yes. Before the computer, that was what most doctors had in clinics to look up information on drugs.
Q. I wonder how their sales are doing these days.
A. I don't know. They still ask me for 60 bucks every year.
Q. Really?
A. I still get a copy. But, you know, truth be told, I actually go to the Internet to get labels.
Q. Then you cite some Bayer internal documents, "Integrated Summary of Efficacy," "Integrated Summary of Safety"; is that correct?
A. Yes.
Q. Some FDA guidance materials?
A. Yes.
Q. And what are the FDA guidance materials? What's their -- why are they important to cite?
A. FDA has hundreds of guidance documents which they've written and they actually publish for comment and modify over time.
The guidance documents represent FDA's current

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thinking on how to comply with different requirements of the regulations and the Food, Drug and Cosmetic Act.
Q. And you think those are pretty good sources of information?
A. I think they are a good source, yes, for -- you know, many times, there's more than one way to comply with the regulation, and there you can see what FDA's current thinking is on, for example, use of epidemiology studies and safety evaluations is a very useful guidance.
Q. Okay. Looks like you rely on some ACOG bulletins or opinions; is that right?
A. Yes.
Q. And what's ACOG?
A. American College of Obstetrics and Gynecology.
MR. JONES: I'm going to go on and mark this supplemental materials list, too, so we don't lose track of that.
(Exhibit Feigal-5 was marked for identification.)
MR. JONES: That's Deposition Exhibit 5.
BY MR. JONES:
Q. Now, back to these invoices, we're at May the 4th or 5th. I can't remember what day it is.
Has an invoice been prepared for the work that

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you've performed for this case during the month of April 2016?
A. No, it has not yet.
Q. Okay. Have you -- when I worked in a law firm and I billed clients, I used to have to submit my time to somebody who would prepare the bills.
Have you done that in this case for the month of April?
A. No, I have not done that yet.
Q. Do you have any idea how much time that you've spent in the month of April working on the pseudotumor cerebri cases?
A. No, I haven't added that up.
Q. Is it less than five hours, more than five hours?
A. Well, it would be more than five hours.
Q. Less than 20? More than 20?
A. It's probably also more than 20. It wouldn't surprise me if it's comparable to the time spent in March, but I don't know exactly.
Q. Okay. And the time spent in March was 41.5 hours.
A. Yes.
Q. Okay. And then what did you do to prepare for your deposition here today?

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A. I reviewed my report; I reviewed some of the materials; I continued to read the materials relating to Dr. Ross's opinions, including his deposition, which I -- if I had it, I had not gone through it in as much detail at the time I'd written the report as afterwards; I spent some of the time with some of the estimates that Dr. Ross had presented from his use of the epidemiologic databases, I spent some time checking those numbers and those systems; talked with attorneys in preparation for this. Those are the types of things I did.
Q. How many times did you meet with Bayer's attorneys in preparation for this deposition?
A. Once.
Q. And when was that?
A. It was last -- I think it was last Thursday.
Q. And how long did that meeting last?
A. Four or five hours.
Q. And since that time, you haven't met with Bayer's attorneys again in preparation for this deposition?
A. No, I have not.
Q. Any telephone conferences with them between last Thursday and today?
A. Yes, I did have a brief, half-hour discussion with the attorneys Monday morning.

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Q. Okay. And --
MR. SCHMIDT: Larry, I don't know if you want to speak or not or just talk to you about it on the break, but there was an earlier meeting that I think he's forgotten.
THE WITNESS: Okay. Thank you.
MR. SCHMIDT: And if you find that objectionable, I won't do that again.
MR. JONES: No. No. No.
THE WITNESS: No. He's right.
MR. SCHMIDT: Trying to help.
THE WITNESS: There were two meetings.
MR. JONES: Okay.
BY MR. JONES:
Q. And now that your recollection has been refreshed, do you remember when the other meeting was other than last Thursday?
A. It was about ten days before that.
Q. Okay.
A. And it was also a four- or five-hour meeting.
Q. Okay.
MR. SCHMIDT: Bless you.
BY MR. JONES:
Q. Have you -- are you aware of how many experts Bayer has designated in these pseudotumor cerebri cases?

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A. No, I'm not.
Q. Have you reviewed any of the reports of Bayer's other experts in these cases?
A. No, I don't believe so. I've reviewed Bayer company documents and depositions but I don't believe I have reviewed any of the other Bayer expert materials.
Q. Have you reviewed any of the deposition testimony of any of the other experts designated by Bayer?
A. No, I have not.
Q. Do you know who Dena Hixon is?
A. Yes, I do.
Q. And how do you know who Dena Hixon is?
A. As I recall, Dena was at the FDA at the same time I was. She was in the Division of Metabolic Endocrine, which then later was split and became the Division of Reproductive and Urological Products.
Q. And when is the last time you talked with or otherwise communicated with Dena Hixon?
A. You know, I don't know if I've ever met her face to face. I just know of her.
Q. And you don't believe that you've ever received Miss Hixon's report in this case?
A. I do not think I have had -- I don't recall ever having seen it.

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Q. My colleague tells me that, according to the stuff on the thumb drive that she's looking at that you provided to us, that you received a copy of Miss Hixon's report on April the 12th, 2016.
A. Oh, then I stand corrected. I haven't looked at it.
Q. So you don't know whether or not her opinions are valid or not?
A. Yes. I don't have any opinions about her opinions.
Q. Between the time you were contacted to consult in the pseudotumor cerebri cases and today, have you ever talked with any Bayer employees?
A. No, I have not.
Q. Have you ever asked through counsel to talk to any Bayer employees?
A. No.
Q. Why not?
A. I thought that the documents produced spoke for themselves.
Q. Do you -- when I say "the Rai study," do you know which abstract I'm talking about?
A. Yes, I do.
Q. Okay. And do you know or have you ever met any of the listed authors of that particular study?

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A. I have not. I actually looked to see -- since both my father and my stepfather were faculty at the University of Utah, two different departments, I did actually look to see if there were any people there that I knew from those contacts. But that's been some time since I've had any contact with the university and -- but I did look up the -- him and the department and mostly focusing on him, not so much the other authors. But I didn't recognize any of the names.
Q. When you say "him," who are you referring to?
A. Or is it a her? Dr. Rai.
Q. Dr. Rai. Dr. Rai, it's a she.
A. Oh, okay.
Q. She's Rai.
A. Okay.
Q. And so that was kind of a long answer. I just wanted to make sure that I understood it.
You do not know any of those authors?
A. No, I -- no, I do not. And I did look up her status as -- and she's a research fellow at the university.
Q. Okay. And have you ever had any contact with any of those authors?
A. No, I have not.
Q. Have you ever attempted, directly or indirectly,

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to contact those authors about their particular study?
A. No.
Q. Have you had any contact with anyone at their university about the study that they have performed?
A. No.
Q. What was your purpose of trying to figure out if you had any contacts at the University of Utah?
MR. SCHMIDT: Object to characterization.
THE WITNESS: It's -- I just wanted to see if there were anybody that I knew, since, as I mentioned, both my father and stepfather were at the university. Both of them were department chairs. So over the years, I've socially met a number of faculty from the medical school at the university and so I was just interested to see if there was anybody that I knew, but I did not recognize any of the names.
BY MR. JONES:
Q. Are you still working on the Mirena MDL case?
A. There's no -- there's been no activity in the -- in recent months but, as I understand it, it will probably become active again at some time in the future.
That's just with respect to my activities. I'm sure that there's activities for some people.
Q. I'm sure the lawyers.
Do you remember how long your report was,

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approximately, in the Mirena MDL case?
A. It was similar in length to this report, although, as I recall, a bit -- you know, perhaps a bit longer.
Q. And in the Mirena MDL case, based upon my calculations, you've been paid to date $100,000 -- $100,600. Does that sound correct?
A. It does sound like it's probably correct, yes, since 2013. Yes.
Q. Now, you have given me an updated testimony list.
Do you have any trial testimony scheduled in the next six months?
A. No.
Q. Have you ever testified in favor of an individual human being who alleged that they were injured by the product of a pharmaceutical or medical device company?
A. I have been engaged in and retained in cases like that. None of them have ever required deposition or testimony at trial. Some are still active and haven't progressed that far, others resolved before testimony was required.
Q. How many of those cases have you worked on the side of the individual person who claimed that they were

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injured?
A. I would estimate there's probably been four or five over the years. There's one that's currently active.
VIDEO OPERATOR: Counsel.
MR. JONES: Oh, thank you.
Are we at about an hour on the video?
VIDEO OPERATOR: Yes.
MR. JONES: We normally take hour breaks so people can have bio breaks.
THE WITNESS: Sure.
MR. JONES: So let's go off the record.
VIDEO OPERATOR: We are going off the record. The time is 10:14 a.m.
(Recess, 10:14-10:27 a.m.)
VIDEO OPERATOR: We are back on the record. The time is 10:27 a.m.
BY MR. JONES:
Q. Dr. Feigal, welcome back from the break.
Before the break, we were talking about, you'd mentioned that maybe you've had four or five clients over the years where they were individuals who alleged that they were injured by a drug or medical device and that kind of got me thinking, none of those are listed on the trial or deposition testimony list; right?

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A. That is correct.
Q. Okay. So in your business there are -- you do have engagements that do not ultimately end up resulting in testimony; is that correct?
A. Yes, that's correct.
Q. Okay. And other than what's listed on your testimony list, since you've been consulting after you left FDA, approximately how many other medicolegal cases have you been involved in in which you were not required to testify in any way?
A. I don't know. I have never really tried to count that up or estimate it. It's -- I would say that more than half of the engagements result in a deposition, at least a deposition, so this may represent, you know, approximately half of the engagements I've had.
Q. Okay.
A. But that's just a rough, rough guess.
Q. And how long have you been doing medical-legal consulting?
A. Since 2005.
Q. Okay. So about 11 years?
A. That's correct.
Q. What percentage of your time in 2015 was devoted to medical-legal consulting?

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A. In 2015 it was approximately 40 percent.
Q. Okay. What about 2016?
A. It's been about 25 percent.
Q. 2015?
A. '15 was --
Q. Or 2014. I'm sorry.
A. Oh, '14. I'm sorry. '14 was probably 30, 35 percent.
Q. And what about 2013?
A. Probably about the same.
Q. And at NDA Partners, L.L.C., is that what it is?
A. Yes. Uh-huh.
Q. What else do you do in the rest of your time?
A. The company's prime focus is actually assisting start-up companies, develop their research plans, their regulatory strategies, assist them in designing the initial studies they need to do for their drugs and medical devices, and assist them in properly writing and submitting, keeping the records of those studies, submitting them to FDA. We participate with those companies in some of their FDA meetings, in others we work behind the scenes.
And there are some companies where we will actually on a contract basis drop in management, if you will. I've been chief medical officer of three

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different companies on a part-time basis on a contract through NDA Partners. We will -- with some of the companies, they're increasingly virtual companies where they don't have a full-time staff and they work -- the company actually consists of contract staff who will actually do actually most of the work for the company. But that's a more recent type of thing we've been doing.

Over the years, we've largely worked with the companies in that early sort of strategic phase where they're trying to get their product started. And we work with their investors as well as with the companies, help investors, due diligence, evaluate products.

Q. In 2015 you said about 40 percent of your time was on medical-legal consulting.

What did you do for the other 60 percent of the time?

A. I worked with small -- I worked with these small companies.

In a typical point in time, I typically have between 12 and 20 active small clients. You know, for example, this morning before this meeting I took a call from one of those clients on a study design issue that they were discussing with their statisticians.

And so it's a lot of -- it's a very interactive process working with these companies as they try and

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move their products forward.

Q. Okay. And how much do you bill those clients per hour?

A. The rate that we have for small companies is billed by the task. We identify a task and then we price that, and it's a fixed price. If it takes less time than that, billed at $500 an hour, they pay the less; if it takes more time, we just do it for the fixed cost.

Q. Okay. Looking at your testimony list, for the last four years it doesn't look like that there have been any updates on the trial testimony. The prior copy that I had had the last trial 9/29 to 10/1/15 and 10/6/15, and that's the same as on the updated list; is that correct?

A. Yes. There have not been any trials this year since that time.

Q. Okay. And let's look at that list. Can you get that list?

THE WITNESS: Can I get the list from you, Paul, prior testimony?

There it is. Yes. Okay.

MR. JONES: Okay.

BY MR. JONES:

Q. Going in reverse chronological order, that was

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the George Decou, D-E-C-O-U, versus Takeda Pharmaceuticals?

A. Yes.

Q. And that was in Nevada; right?

A. Yes, it was.

Q. Okay. And how many days did you testify at that trial?

A. That trial settled during my testimony so they probably weren't done with me, but I testified on the 29th, the 1st, and the 6th. So I testified on three days and we still weren't done.

Q. Okay. And that was an Actos case --

A. Yes.

Q. -- like we talked about earlier?

A. Yes, it was.

Q. Okay. Then the one going up before that, Pericor Therapeutics versus Merck, that looks like that was a Triple A arbitration?

A. That's correct. That was a --

Q. Okay.

A. That was a business dispute between Merck and another company.

Q. Right.

Going up before that, Kevin Phillips versus C.R. Bard, 2/5/2015, what was that case about?

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A. That was a case that was -- involved an alleged injury from a medical device, an inferior vena cava filter.

Q. IVC?

A. Yeah, IVC.

Q. And what were -- well, did you testify in that case that the company properly warned its users of the risks?

A. Actually, not. In that case I was actually an epidemiology expert and so I provided testimony about what was known from the medical literature about the performance of various IVC filters and whether or not accurate estimates were available about rates of different complications.

Q. Okay. And the jury verdict in that case was about $2 million; is that correct?

A. I don't know.

Q. Okay. Let's go up to the next one, Kristufek, K-R-I-S-T-U-F-E-K, versus Takeda Pharmaceuticals.

That one looks like it was in Philadelphia; is that correct?

A. Yes, it was. Uh-huh.

Q. Okay. Was that an Actos case as well?

A. Yes, it was.

Q. And it looks like you testified on three

different days during that trial?
A. I did.
Q. Is that three full days?
A. I think it was two half days and a full day.
And, as you notice, the -- you may notice, the Phillips trial was going on at the same time, so I had to -- I had to go from Philadelphia to Nevada and back.
Q. Oh, wow.
A. It was a -- it was a busy week.
Q. I didn't notice that, but you're right.
And in that case the jury awarded approximately $2.3 million; correct?
A. I don't know.
Q. The next one up, the Drakes versus Allergan in the District of Vermont, what was that case about?
A. That case related to the drug Botox used to treat spasticity from cerebral palsy and an allegation that a seizure disorder had been caused by the Botox injections.
Q. And what was your role in that case?
A. To evaluate the evidence for the association between botulinum toxin and seizure disorders and the accompanying warnings in or considerations for warnings in the product labeling and the interactions between the company, FDA, and the European authorities on that

topic.
Q. Okay. So at a high level, kind of like what you're testifying to in this case?
A. Yes, at a high level.
Q. Okay. And isn't it true that the jury awarded approximately 6.5 million in that case?
A. I remember there was a plaintiffs' verdict. I don't -- I don't know the amounts.
Q. Okay. The next one up, Myers versus Takeda Pharmaceuticals in West Virginia, do you remember that?
A. I do.
Q. Okay. Was that also an Actos case?
A. It was.
Q. And in that case, according to my research, there was a defense verdict but the plaintiff was awarded $155,000 because the company had destroyed documents.
Were you aware of that?
A. I was aware of that jury and that award, yes.
Q. The next one up, Wisniewski, W-I-S-N-I-E-W-S-K-I, versus Takeda Pharmaceuticals in Philadelphia, was that another Actos case?
A. Yes.
Q. And in that case the jury awarded approximately $2.14 million; is that correct?

A. Again, I don't know. I don't -- usually I don't keep track of the awards, and I also realize that there are some negotiations and settlement process that changes those from the time of the trial. So I -- sometimes I know, but usually I don't know what the results are.
Q. Tersigni, T-E-R-S-I-G-N-I, versus Wyeth Pharmaceuticals and Pfizer in the District of Massachusetts, do you remember that case?
A. I do.
Q. And what was the drug at issue in that case?
A. The drug was fenfluramine and dexfenfluramine.
Q. Is that Fen-Phen?
A. Yeah. It's part of the -- one of the fens. Yeah.
Q. Oh, it's just one of the fens?
A. The other is phentermine.
Q. And my research tells me that there was a defense verdict in that case.
Does that sound --
A. Yes, I believe there was.
Q. Then going above that, Diane Whitlatch, W-H-I-T-L-A-T-C-H, versus Takeda Pharmaceuticals in Cook County, Illinois, do you remember that case?
A. Yes.

Q. Okay. And that was an Actos case?
A. Yes, it was.
Q. Okay. And in that case was there a defense verdict?
A. I don't recall.
Q. In fairness to you, I believe that there was --
A. Oh, okay.
Q. -- based on my research.
Going above that, In Re: Actos. This would be Allen, A-L-L-E-N, versus Takeda Pharmaceuticals in the Western District of Louisiana.
Do you remember that case?
A. I do.
Q. And you testified for two days in that case?
A. I did.
Q. And at a high level, you testified that the warnings were appropriate and that the interactions were -- with FDA were appropriate; is that correct?
A. Yes. At a high level, that's correct.
Q. Okay. And in that case the jury awarded $9 billion; is that correct?
A. It was a large amount, later reduced, but I don't know where that finally settled. But it was -- it was a large amount.
Q. The next one is Kendall versus Hoffmann,

H-O-F-F-M-A-N-N, in Atlantic City, New Jersey.
Do you remember that case?
A. Yes, I do.
Q. What was that? Was that an Accutane case?
A. Yes, it was.
Q. And what did you -- at a high level, what did you testify about in the Accutane case?
A. I testified about the adequacy of the warnings for inflammatory bowel disease and the appropriateness of the changes to the labeling that occurred over time.
Q. And in that case the jury awarded approximately 1.58 million; is that correct?
A. Again, I don't know.
Q. Okay. Above that, Alen versus Takeda Pharmaceutical in Nevada.
Do you remember that case?
A. I do.
Q. Okay. And that was an Actos case?
A. It was.
Q. And that was a defense verdict in that case; correct?
A. I do recall that, yes.
Q. Okay. The next one, Camhong, C-A-M-H-O-N-G, last name, A-N, versus Takeda Pharmaceuticals in Baltimore City, Baltimore, do you remember that?

A. Yes.
Q. And was that an Actos case?
A. Yes, it was.
Q. And in that case the jury awarded approximately 1.7 million to the plaintiff?
A. Again, I don't know.
Q. Okay. Going above that, Fleischmann, F-L-E-I-S-C-H-M-A-N-N, versus DJO, Inc., in San Diego County, do you remember that case?
A. I do.
Q. And was that a pain pump case?
A. No. It was a -- it was a cold therapy device. It was a device that would wrap around the knee and -- or the shoulder or whatever orthopedic part that was -- had been surgery and would cool the -- cool the joint to treat pain. But --
Q. Okay.
A. But strictly through cooling.
Q. Okay. And my research says that was a defense verdict.
Do you remember?
A. Yes, I believe that's correct.
Q. Okay. The next one, Delores and Milton Tietz, T-I-E-T-Z, versus Abbott Labs, in Cook County, Illinois, do you remember that one?

A. Yes, I do.
Q. And what was the -- what drug or device was involved in that one?
A. The drug was a drug called Humira, H-U-M-I-R-A, and it was an allegation that there was an injury associated with the use of that drug.
Q. Okay. And at a high level, did you testify about the adequacy of the warnings and the company's involvement with the FDA?
A. Yes, I did.
Q. Okay. And the plaintiff was awarded approximately 2.2 million in that case?
A. As I recall, there was a plaintiffs' verdict, yes. I don't know the amount.
Q. Okay. Then we -- above that we have Cooper versus Takeda Pharmaceuticals in San Francisco County; is that correct?
A. Yes, that's correct.
Q. I'm a little confused because under the date it says Los Angeles, California. Is that right?
A. You know, it may be -- I think the San Francisco is wrong. I think it's Los Angeles. Because I don't remember testifying in San Francisco.
Q. Okay. And was that an Actos case?
A. Yes, it was.

Q. Okay. And in that case the jury awarded approximately 6.5 million to the plaintiff?
A. Again, I don't recall.
Q. Okay. Going above that, In Re: Gadolinium, this is the Decker versus GE Healthcare case in the Northern District of Ohio.
Do you remember that case?
A. I do.
Q. And what is gadolinium?
A. Gadolinium is a drug that's given intravenously and allows you to visualize vascular structures and -- on MRI scans and to -- it highlights different tissues in different ways so it's used largely to detect brain tumors and other types of abnormalities like that.
Q. And what did the plaintiffs allege in that case?
A. They alleged that there had been an injury from the gadolinium that had caused a very severe rheumatologic disease.
Q. And what was your role in that case?
A. It was evaluating the signal detection, the evaluation of the initial evidence that the gadolinium contrast agents were related to this syndrome, and then a testimony on the nature and -- of the company's interactions with FDA in updating their labeling.
Q. Was your client GE in that case?

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A. Yes, it was.
Q. I used to represent GE too.
A. Oh.
Q. The plaintiff -- the jury awarded the plaintiff approximately 5 million in that case?
A. I don't know the amount, but I do recall it was a plaintiffs' verdict, yes.
Q. Okay. Going up next, we have an arbitration hearing, Eagle Pharmaceuticals versus The Medicine Company.
Was that a business dispute?
A. It was.
Q. Okay. Going next, we have Reynolds, Wilkinson, Young, Rossitto, R-O-S-S-I-T-T-O, versus Hoffmann in Atlantic County, New Jersey.
Do you remember that case?
A. Yes, I do.
Q. Was that an Accutane case?
A. Yes, it was.
Q. Was there a defense verdict in that case?
A. As -- there were four plaintiffs. As I recall, there were both defense and plaintiffs' verdicts in that case.
Q. Mixed bag?
A. Mixed, yes. Two -- it was two defense and two

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plaintiffs, as I recall.
Q. Okay. Then going up to 5/23/12, the Everetts versus C.R. Bard in Maricopa County, Arizona.
Do you remember that case?
A. I do.
Q. Was that an IVC case?
A. Yes, it was.
Q. And do you remember whether there was a defense verdict in that case?
A. I don't recall.
Q. Other than IVC, Accutane, gadolinium, Actos, Humira, Fen-Phen, and Botox, what other drugs or medical devices have you given testimony on in your consulting career?
A. Well, that would be reflected in the deposition testimony in the remainder of the report.
Q. Okay. So it might help you if we go through some of that?
A. Okay. Do you want to go front to back or back to front?
Q. Well, let's see. Let's start on -- let me make sure that I'm on the right page with you.
A. I mean, if you want, I could actually walk down through them and just briefly describe them.
Q. Yeah. Yeah.

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A. Describe them.
So starting in 2012, there's a case where I represented plaintiffs who had a dispute with BlueCross, and we had a settlement in that in which case the plaintiffs got their bills paid. BlueCross ended up paying.
Q. What was the nature of that dispute?
A. BlueCross had denied payment for an artificial intervertebral disk that I think over 40 plaintiffs had had placed and had either bills or paid for out of their own pocket.
BlueCross stated that they declined to pay for it because it was an investigational product but, in fact, it was an approved product and it was used on label and it had been approved for about eight years. So --
Q. Okay.
A. -- that was the -- I was -- I played a small role in just saying whatever else BlueCross has the authority to pay for or not pay for, this was not an investigational product.
Q. Okay. Treadwell v. Allergan.
A. So this is a Botox case involving a series of alleged injuries that probably were -- I actually don't remember the exact details of the plaintiff's injuries

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but --
Q. Is it basically the same as the Botox case that you testified at trial about?
A. No. You know, each of the Botox cases have been slightly different. All of them have the common theme in it that it's a patient who has a neurologic condition that they feel is associated with their Botox use but in each case it was a different neurologic condition.
Q. Okay. In Re: Cold therapy cases, what was that about?
A. Those are the cases that show up in trial with DJO with --
Q. Oh.
A. -- with alleging injuries from a cooling device.
Q. The wrap; right?
A. Yeah, the wrap.
Q. Okay.
A. The cooling wrap.
Q. Dalton versus Animas Corporation. That's in Louisville, my neck of the woods.
A. It is. That was a case involving an insulin, insulin pump that -- and alleged injury from a pump which discharged more insulin than was intended so --
Q. Was that -- who had that case? Greg Bubalo?
A. I don't think so. I know Mr. Bubalo, but I

don't believe that he was involved with that, with this particular case.
Q. You know him from the Fen-Phen; right?
A. Right. That's correct. Yeah, that's correct.
Q. Next, Calisi, C-A-L-I-S-I, versus Abbott Labs?
A. This was a Humira case.
Q. Okay.
A. Eagle is -- Eagle and gadolinium we've talked about. Cooper --
Q. Right.
A. -- we've talked about.
The Wells is a case where I wasn't called to testify at court, but it involved another child with cerebral palsy --
Q. Okay.
A. -- and Botox.
Q. Was that -- is that the -- no. What drug was involved for that? Oh, Botox. Okay. Got you.
A. Yeah, this was Botox.
Bard, this was a case where I was an epidemiologist offering testimony in epidemiology about what was known about the use of surgical mesh and pelvic.
Q. Is this the -- okay. Have you testified -- you haven't testified in any of those mesh cases?

A. Not in court. I've provided a deposition but not in court.
Q. And what company did you work for? Did you work for Bard in that case?
A. I was asked to provide these by attorneys for, yes, C.R. Bard.
Q. Okay.
A. Yeah.
And An, the next case, we've talked about.
The next page has a deposition for Fen-Phen that's related to I'm not even sure which cases.
Q. That's okay.
A. The --
Q. Brown?
A. Yeah. I don't -- I guess --
Q. Is that a med-mal case?
A. You know, this reference looks incomplete. I can't quite tell which case this is. You know, I have not done very many med-mal, but I don't recall this case.
Q. Okay. And we have Actos.
A. Then we have, yeah, more Actos. The Wendell is -- I would have -- is probably a Humira case but I'm not sure.
Q. Do all of those companies there -- what's their

involvement with Humira?
A. All of those cases -- all of those companies make TNF-alpha inhibitors, and I think this was a patient who had been on four or five different drugs in the class.
Q. Got you.
A. As I recall.
Then there was an inferior vena cava, a deposition relating to Accutane and inflammatory bowel disease.
The next two are on the -- result also in trial testimony.
The case involving Gates was with the da Vinci robotic surgery device made by Intuitive.
Q. What was your role in the da Vinci case?
A. As a medical device expert on manufacturing and design standards that companies have to meet and what was known about the problems with, basically, the FDA aspects of the approval of products like that.
Q. Okay. And the Willoughby case?
A. The Willoughby case was a med-mal case that also cited the hospital engineer, which was an employee of, a contract employee of General Electric, one of their companies. And so I offered opinions on the proper role of and the responsibilities of hospital engineers, as

opposed to device manufacturers. The injury was caused by a malfunctioning surgical table.
So the Drake case we've discussed.
The next Bard cases are IVC, deposition relating to inferior vena cavas.
We've talked about Brunston and --
Q. Now, on the Campbell case --
A. Yes.
Q. -- it says it's in Scott Circuit Court in Kentucky.
Do you remember who the attorney was who took your deposition in that case?
A. I don't.
Q. Okay.
A. There are some memorable ones but I don't recall in that case.
Q. Okay. Brunston versus Guy versus Bayer HealthCare?
A. I believe this is a deposition relating to Mirena but I'm not sure. But I -- I'm not sure which -- if that's the case.
Q. Let me ask you -- let me stop you for a second.
Other than the Mirena cases, have you ever served as an expert for Bayer?
A. I have evaluated other product issues. I can't

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remember if they came to depositions and if this is one of them.
Q. Okay.
A. And I don't recall at this point what they were.
Q. Have you ever worked with the attorneys from Covington & Burling before on any of the other cases?
A. Yes, I have. With the Accutane cases.
Q. Okay. Anything other than Accutane?
A. I believe the Covington attorneys have -- well, I'm not sure. I can't remember if they also had a role in some of the Actos trials or not.
Q. And what about the attorneys from Shook Hardy Bacon; have you ever worked with those --
A. Shook --
Q. -- with that firm before?
A. Shook Hardy had -- some of their attorneys had a role in some of the Actos cases as well.
Q. What about Goldman Ismail; have you ever worked with them before?
A. There is a partner, there is a firm in Los Angeles where one of the names in the firm is Ismail. I'm not sure if it's the same -- if it's the same firm. But I have worked on -- yes, I have worked on -- if it's the same firm, I have worked on cases with them.
Q. What kind of cases?

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A. As I recall, these are probably on this list as a deposition for -- relating to Lexapro and Celexa.
Q. Okay. What about, have you ever worked with a firm called Bartlit Beck?
A. Yes. Bartlit Beck I believe were the attorneys in Chicago that represented Allergan in the Drake case.
Q. Okay.
A. So finishing up the list, the Zimmer Nexgen knee, this was a case involving knee implants, and I offered testimony on a manufacturer's responsibility to evaluate their product prior to approval and once on the market.
Q. What about Jones v. Pfizer, which is right above that? I think we skipped that.
A. Yeah, we did.
What I don't recall, that may have been a -- that may have been a Fen-Phen case, since they acquired Wyeth. So I don't remember. I'd have to go back and look to see if that was a Fen-Phen case. But I believe that's what it may have been.
Q. Larson v. Abbott?
A. That would have been a Humira case.
Q. In Re: AlloDerm, AlloDerm case.
A. This was a dispute over a banked human tissue product that was actually called AlloDerm, and it -- my

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role is to -- largely as a rebuttal witness to plaintiffs' witness who asserted that the company was required to meet certain device requirements but, in fact, they are not because it's a banked human tissue. So I did a deposition for that.
Q. Okay. Enoch, E-N-O-C-H, v. Forest Research Institute?
A. This is a deposition about Lexapro and Celexa.
Q. Good v. Pfizer Wyeth, is that Fen-Phen?
A. Yes, it is.
Q. Then we have the Mirena migration/perforation case.
You gave a deposition on October the 20th, 2015; is that right?
A. Yes, that's correct.
Q. And then we have U.S.A., State of California, Colorado, ex rel., Alex Booker and Edmund Hebron versus Pfizer.
Is that a qui tam case?
A. I believe it was, yes.
Q. And who did you serve as an expert for in that case?
A. For Pfizer.
Q. And that's obviously been unsealed; correct?
A. You know, I don't know the status of that.

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Q. The next one, Sherrer versus Truman Medical Center, Boston Scientific, C.R. Bard, is that a transvaginal mesh case?
A. I believe so, yes.
Q. Okay. The next one is Forsta, F-O-R-S-T-A, AP, A-P, hyphen, F-O-N-D-E-N and Danske, D-A-N-S-K-E, Invest Management A/S individually and on behalf of all other similarly situated plaintiffs versus St. Jude Medical, Inc., and others.
What's that case about?
A. It's a shareholder suit about -- alleging that there was information that the Saint Jude Corporation should have disclosed.
Q. What -- who do you serve as an expert for in that case?
A. I was an expert on behalf of Saint Jude.
Q. The next one is Bartolini, B-A-R-T-O-L-I-N-I; Raquel, R-A-Q-U-E-L; McGuinness, M-C-G-U-I-N-N-E-S-S, hyphen, Colin, C-O-L-I-N, versus Abbott.
What's that case about?
A. That case involves the drug Depakote and the issue of birth defects.
Q. And what is your -- what's your role in that case? What kind of testimony are you giving in that case?

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A. As a safety expert on safety labeling and warnings and the relationship between the evolving evidence over time and the adequacy of the label -- labeled warnings.
Q. So I'm looking at your report, and you say you served as an expert consultant on regulatory matters under the jurisdiction of the United States Food and Drug Administration, as an expert clinical epidemiologist, and on matters related to pharmaceutical products, the pharmaceutical industry, and other areas within my expertise as described below; is that correct?
A. Yes.
Q. Okay. So what do -- what subject matters do you intend to offer an expert opinion in in these cases?
A. Well, I think it's probably easiest to start perhaps with my general, you know, principle conclusions near the end of the report at 51.
Q. Well, can I interrupt? Maybe I can --
A. Sure.
Q. -- shortchange this.
A. Sure.
Q. It's probably a poor question.
A. Okay.
Q. Are you purporting to offer an epidemiology expert opinion in this case?

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A. Yes, as an -- as epidemiology applies to evaluating evidence for inclusion in the product labeling and the adequacy of warnings.
Q. Okay. And you are providing expert testimony as -- in an FDA regulatory capacity as well; correct?
A. Yes, that's correct.
Q. Are there any other areas, areas of expertise, that you claim besides epidemiology and FDA regulatory issues?
A. Well, it relates to the regulatory areas, but I am an expert on safety communications and warnings, whether they come from companies or from FDA and whether they're required by FDA or not.
Q. And your report that you've submitted, the substance of it is 52 pages long; correct?
A. That's correct.
Q. Okay. And these are the opinions that you're going to be giving in this case; correct?
A. Yes; to a large extent. There may be things that come up today or that come up in reaction to things that developed after the report, such as other depositions, but I don't think any of them have required me to amend this report. I think this report does cover the areas that I intend to offer opinions about.
Q. Okay. Well, this is my only opportunity to depose you and find out what your opinions are going to be when we get to the trial of this case, and so are there any opinions that you have about this case that you did not include in your 52-page report?

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A. Generally speaking, no. There may be things that I would be asked an opinion about that isn't word for word contained in the report, but they would all be related to opinions in the report. So you can rely on the report as the basis for my opinions.
Q. Okay. And you did a really nice job of putting together a table of contents, which makes it easier to kind of flow through it.
Section I is your qualifications; is that right?
A. That's correct.
Q. Okay. And then Section II is titled "FDA Requirements and Review Practices," and under that are various subheadings; correct?
A. That's correct.
Q. But, by and large, would you agree with me that the information contained in Section II is basic background information on FDA processes for drug development and drug labeling?
A. Yes, it is. It's tailored to the issues in this case. So there have been sections in other reports that I didn't include here that weren't at issue here. And

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because there were many issues around pharmacovigilance, the pharmacovigilance in this section is written with this case in mind.
But it is general background. It's stuff, it's materials that would apply to -- generally, to all products in a similar situation, looking at a safety issue developing after approval.
Q. Okay. And then Section III, you discuss Mirena specifically and the IND and NDA approval; correct?
A. That's correct.
Q. So you start getting more specific in Section III.
A. That's right. And that section, Section III, is basically the background, the type and size of studies that led to the approval and what was known at the time, and so that also is general in the sense that it doesn't really dig down in yet to the issues around IIH.
Q. Okay. And then Section IV is titled "Idiopathic Intracranial Hypertension"; right?
A. Yes, that's right.
Q. And you don't claim to be an expert in idiopathic intracranial hypertension, do you?
A. No, I'm not. I mean, in the days when I was seeing patients, I took care of a patient with pseudotumor cerebri, as we called it back then, but I'm

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not an expert -- I don't -- I'm not offering myself as an expert on that condition.
Q. When is the last time you treated any patients?
A. I still am actively licensed, but I have not been seeing patients since 1992, when I went to FDA.
Q. Okay. And how many years were you seeing patients before 1992?
A. As a licensed physician, from 1977 through 1991.
Q. And did you serve in -- I looked at your CV.
It looks like you had a lot of administrative responsibilities during those years; correct?
A. Well, I had my share.
I was the residency coordinator for a couple of years and I was an epidemiology program director and I was a director of quality-assurance at San Francisco General Hospital, but I also had a very active faculty practice as a member of, you know, three medical schools I was faculty at and saw patients on a regular basis in the house staff and student and fellows' clinics and was an attending on the hospital services, including the consult services for other disciplines, approximately four months of the year.
So I would say probably about half my time as an academic was spent in clinical care of patients or patients of the house staff I supervised.

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Q. You're smiling because you anticipated my next question, which was what percentage of the time?
During those years when you were working at the hospitals, how many patients did you diagnose with pseudotumor cerebri?
A. I can recall one.
Q. Okay. How many patients during that time did you treat for pseudotumor cerebri?
A. We treated that patient. That patient remained on my medical service with neurology consultants and neuro-ophthalmologists acting as consultants.
We treated her as -- it's an unusual enough condition that I can't claim to remember all my patients but, as I recall, we treated her with diuretics and repeated lumbar punctures.
Q. Do you remember what caused that particular patient's pseudotumor cerebri?
A. I don't think we knew. She was a patient who was obese and a patient who had taken tetracycline, but I don't think we knew.
Q. And at least in some medical literature tetracycline has been associated with the development of PTC; correct?
A. Yes. I haven't critically reviewed that literature, but that is one of the drugs that's

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discussed as a potential cause.
Q. Then Section V of your report is titled David Ross's, "Dr. David Ross's Report."
Do you see that?
A. Yes.
Q. Okay. And then is it fair to say that what's in that report or what's in that section of your report is your criticisms of Dr. Ross's expert report in this case?
A. Yes, it is.
Q. And you know Dr. Ross from FDA; right?
A. Yes, I -- he -- I was responsible -- I was responsible for the division he was part of and I was the director of that division for a year and remember working with him as he reviewed a supplemental application for a New Drug Application that year, so actually I knew Dr. Ross fairly well.
Q. What drug was that?
A. It was -- you know, I forget which drug it was. It was a -- as I recall, it was a cephalosporin, an antibiotic, and the indication was, I believe, a novel indication, which was to prevent infections in patients getting cancer chemotherapy.
Eventually, that drug didn't need to be used anymore because growth factors could be used to raise

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white counts to prevent the infections.
Q. Uh-huh.
A. But in the day and when I was practicing, that was the most common cause of death in cancer patients was infections complicating their chemotherapy.
So that was quite an important new indication, and he was the primary reviewer for that.
Q. Okay. And what -- you said you were the head of that division?
A. That's correct. I was the director of the Division of Anti-Infective Products, which is where he was working in probably about 1994, 1995. I don't remember exactly.
Q. And how much interaction would you have with Dr. Ross?
A. Well, a fair amount. As a division director in the division, as I recall, we may have had not more than a dozen physician reviewers and we would make rounds, if you will, on our drugs, talk about the drugs that were being evaluated that the physician reviewers had responsibility with.
They usually had the lead responsibility for the clinical aspects of the drugs. The teams also included other disciplines like toxicologists and pharmacologists. But I would have had almost -- you

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know, certainly every week and almost -- in some time periods, you know, several times a week direct interactions with Dr. Ross.
Q. Did you get along with Dr. Ross?
A. Yes.
Q. Was he a good employee?
A. For the year I worked with him, I thought he did a very good job, yes.
Q. Do you think he's smart and competent?
A. Well, you know, my direct experience is limited to that year and that review, but I thought he did a good job.
Q. Okay. Do you think he's smart and competent?
A. I think he is smart. You know, competent is just a little too broad. I think you'd have to talk about specific work products or specific opinions and things. I don't think he and I would always agree.
Q. You don't think that the two of you would agree or you and I would agree?
A. He and I would agree.
Q. Okay.
A. I don't know about you.
Q. Did you guys ever have any conflict with one another?
A. Not that I recall.

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Q. Did you ever sanction him, punish him, write him up for any sort of deficiencies in his work product at FDA?
A. No.
Q. Then the next section, Section VI, is "Dr. Mayhar Etminan's Report," and it looks like you spend between Page 45 and 48 on your criticisms of his report; is that correct?
A. That's correct.
Q. Okay. And I don't -- did you know that he is not going to be an expert in this case?
A. Yes, I was informed that he withdrew.
Q. Okay. So we will probably not talk about that today, which may make you happy.
A. I'd be happy to talk about it, but since he's withdrawn --
Q. Well, I know. But it will be shorter.
A. No. I'm --
Q. Shorter is happier for everybody.
A. Shorter is good.
Q. Okay. And then it looks like you spend Page 50 criticizing Dr. Fraunfelder's report; is that correct?
A. Well, I make comments about it, yes.
Q. Make comments?
A. Yes. I mean, I don't -- yes, I make criticisms

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of his report. Yeah, that's what these three sections are about are my criticisms or comments on points that they're making.
MR. JONES: Okay. Jumping back up for a second, we're two minutes until the video ends, and I don't think I can get a question out and an answer in two minutes.
THE WITNESS: All right.
MR. JONES: So let's go off the record, take a short break, and we'll come back to it.
VIDEO OPERATOR: We are going off the record. This is the end of Media Number 1.
The time is 11:17 a.m.
(Recess, 11:17-11:31 a.m.)
VIDEO OPERATOR: We are back on the record. This is the beginning of Media Number 2, and the time is 11:31 a.m.
MR. JONES: Excuse me.
BY MR. JONES:
Q. Dr. Feigal, we're back on the record after a break.
Let's go to your CV.
A. Sure.
Q. Talk about it for a second.
A. Okay.

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Q. Okay. We talked already about your experience prior to 1992.
It looks like you went to the FDA beginning in 1992.
A. That's correct.
Q. And what was your position in 1992 when you started at FDA?
A. My initial position was I was a director of the Division of Anti-Viral Drugs.
Q. Okay. And that was in the Center for Drug Evaluation and Research?
A. That's correct.
Q. And what did you do as the division director for anti-viral drug products?
A. Our division was one of nine divisions that divided up the drugs that are on the market and the drugs -- and also the drugs that are in testing.
So I had responsibility for all of the drugs for AIDS and influenza and herpes infections and as well as drugs for fungal infections and tuberculosis. Basically, all the non-sort of bacterial infections. We also had the transplant drugs in our division.
So as the division director, I was responsible for both the investigational phase and the post-marketing phase for the drugs we were responsible

for.
Q. And how many employees did you have working for you in the Division of Anti-Viral Drug Products?
A. When I started, there were 60. Within a couple of years, it was up closer to 120.
Q. Okay. And did your division include any contraceptive products?
A. It did. We had responsibility for the topical contraceptives, such as nonoxynol-9 that was used in contraceptive foams and is used with coating on condoms.
Q. Okay. Any others?
A. Those were the principal ones.
Q. Okay. And was that a product that was approved as a new product while you were the director for the Division of Anti-Viral Drug Products?
A. No. It was an old product and, largely, an OTC product. But we were very actively involved with contraception and -- because of the interest in providing ways of preventing HIV transmission during sex, which is how it's usually transmitted, and so I served on a number of groups that evaluated contraceptive methods and contraceptive studies during those years.
Q. Okay. Then -- so you started as the director of that division in '92?

A. Yes, that's correct.
Q. And stayed in that position until '96?
A. Yes. I held some positions concurrently but I was the division director from, yeah, 1992 through 1996.
Q. And what -- you held positions concurrently in the period between '92 and '96?
A. Yes. So --
Q. What positions?
A. Well, I was the director of the Office of Drug Evaluation-IV from 1995 through 1997. And so the structure at FDA is that the new drug divisions report to one of five office directors and the office directors have -- supervise the division directors. So I concurrently held both the office position and was at any given time the director of one of my divisions.
Q. And what products or what types of products did the Office of Drug Evaluation-IV regulate?
A. That office had responsibility for all types of infections, not just the viral and the tuberculosis and fungal that I talked about before, but it was all the anti-infective products.
It was about -- it was a very large group of drugs. It was about a quarter of the drugs on the market were our responsibility.
Q. And it included OTC products?

A. It could. It was -- there was an OTC drug division as well, and so there was a joint responsibility between the OTC group and the new drug groups.
Q. Okay. And you did -- so you were in those positions.
By '97, had you given up the position of director Division of Anti-Viral Drug Products?
A. Yes. In '97 I moved from the Center for Drugs to the Center for Biologics, where I was the deputy medical -- deputy -- the medical duty director, center director.
Q. And then take me to '97 to '99. What did you do at FDA then?
A. So in '97 to '99 I was the medical deputy center director in Biologics. I was the second, if you will, in support of the center director for Biologics and I also had organizational units that directly reported to me, including the epidemiology, biostatistics, the pharmacovigilance programs, advisory committees. So I had a role as a deputy and then some direct responsibility, organizational responsibilities.
Q. Going back to the Office of Drug Evaluation-IV, currently, the FDA website says the Office of Drug Evaluation-IV includes three divisions: The Division of

Nonprescription Drug Products, the Division of Medical Imaging Products, and the Division of Pediatric and Maternal Health.
Is that the same structure as it was back in 1995 to 1997?
A. No. They've renumbered the offices and now the office that I formerly had is -- because all of the drugs are for infections, it's called the Office of Anti-Infective Drug Products, I think is the name of the office. So that's -- most of the offices just have a number --
Q. Uh-huh.
A. -- but my old office was named after the products, since they're -- all the products were pretty much in one area.
Q. So today that particular office doesn't have a number assigned to it?
A. That's right.
Q. I'm just trying to understand the structure.
A. Yeah. No. That's right. No. It's a little -- it's a little irrational, but the others are all numbered and then there's that office which actually just has -- is called the Office of Anti-Infective Drug Products, as I recall.
Q. Okay. So from '92 to '97 you were part of the

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Center for Drug Evaluation and Research, the CDER; correct?
A. That's correct.
Q. Okay. And then '97 to '99 you moved over to the Center for Biologics Evaluation and Research, the CBER; correct?
A. That's correct.
Q. And that's a different division, obviously.
A. Yes. It's a -- there are three medical product groups that report to the commissioner, Center For Drugs, Biologics, and Devices. All of them have slightly longer names than that, but those are the three categories you can think about.
Q. Okay. And then the devices, from '99 to 2004 you served in the Center For Devices and Radiological Health; right?
A. Yes, that's right. I was the director on this one.
Q. Okay. So that, the Center For Devices and Radiological Health, they don't regulate drugs in that division; correct?
A. No. If they're -- if the product is regulated as a drug, it's in CDER, but there are combination products and drug delivery devices, some of which are regulated in the device center.

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Q. That's a good point.
You're familiar with the Mirena product; right?
A. Yes.
Q. And it's a -- is it a combination product?
A. It is, yes.
Q. Okay. Because it's a device that releases a synthetic progestin drug; correct?
A. That's correct.
Q. And so does Mirena come under the guise of the -- under the regulatory authority of the CDRH or the CDER?
A. It's the responsibility of CDER and it has an approval as a drug.
Q. Okay.
A. The contraceptives that have no drug action, like the old Lippes Loop and the Dalkon Shield, were regulated as devices.
Q. What about, do you know what ParaGard is --
A. Yes.
Q. -- the copper IUD?
A. Yes.
Q. Is that under CDRH or CDER?
A. You know, I always have to look that up, but I think it's regulated as -- I think it's regulated in CDER but I have to look it up to be sure.

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I can make the case it belongs in either, but the copper is thought to have a drug-like effect and that's the rationale for that it's different than just a plain plastic IUD.
Q. Were you ever -- during your time at FDA between '92 and 2004, were you ever personally involved in any part of the regulatory action related to Mirena?
A. No.
Q. During your time at FDA between '92 and 2004, were you ever personally involved in any aspect of regulating ParaGard?
A. No.
Q. Have you ever written any medical articles related to the Mirena product?
A. No, I have not.
Q. Have you ever personally been involved in any epidemiology studies involving the Mirena product?
A. No, I have not.
Q. During your time at FDA between '92 and 2004, were you ever involved in any way with the Norplant product?
A. No, I was not.
Q. Have you ever written any medical articles related to the Norplant product?
A. No.

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Q. Have you ever conducted any epidemiology studies related to the Norplant product?
A. No, I have not.
Q. Have you ever written any medical articles related to levonorgestrel?
A. No.
Q. Have you ever been involved in, personally involved in, any epidemiology studies involving levonorgestrel?
A. No, I have not.
Q. And in preparing your report in this case, you didn't engage in any sort of epidemiology studies related to Mirena or Norplant; correct?
A. Not in the usual sense of that.
I did independently use some of the same tools that the plaintiffs' experts used to look at the epidemiology of the reporting of IIH associated with different products using software such as OpenVigil, which both Drs. Ross and Etminan used.
Q. But you didn't develop any of your own methods to study the epidemiology or any sort of relationship between Mirena and pseudotumor cerebri?
MR. SCHMIDT: Objection. Vague.
THE WITNESS: I didn't develop new methodology. I used my knowledge of epidemiologic methods to evaluate

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the existing literature and the evidence that's available through post-marketing surveillance.
BY MR. JONES:
Q. And you did that for purposes of criticizing plaintiffs' experts' methodology and results in this case; correct?
MR. SCHMIDT: Object to characterization.
THE WITNESS: Well, that's probably where I summarized it in my report but it would have been relevant for me to do that proactively even if they hadn't used those methods. The tools they were using were appropriate, even if I disagree with exactly how they used them or their conclusions.
BY MR. JONES:
Q. So the tools were appropriate?
A. Yes, for evaluating reporting rates the OpenVigil tool is an appropriate and -- convenient and appropriate tool for constructing the kinds of tables and analyses that are used in pharmacovigilance.
Q. So is it fair to say that your criticisms are of the data that they inputted into these tools?
A. The criticisms are the way that they made their selection of how to construct the tables rather than the software that generated the tables.
Q. Have you ever heard the -- strike that.

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Okay. So you left FDA in 2004 and went to NDA Partners, L.L.C.; correct?
A. That's correct.
Q. And was NDA Partners, L.L.C., in existence at that time or were you a founder?
A. I'm almost a founder. It was -- it had been in existence about six months and it was just getting started and organized. But they've taken to calling me a founder now but in the early days they were -- they pointedly reminded me that I joined late.
Q. Yeah, that happens. But six months is -- I'm with you. You should be designated as a founder.
How did you hook up with these folks to get started in NDA Partners, L.L.C.?
A. Well, after leaving FDA, we -- I left FDA, my wife and I had -- she'd at the National Cancer Institute, I had worked at the FDA.
She got a great job with a new research institute in Phoenix, Arizona, and when I moved to Phoenix, Arizona, I didn't find a university that had -- there was no medical school in that town, at least there wasn't then, and there wasn't any other -- I thought I would go back to university and go back to teaching but there really wasn't something that was a good fit for me so I began looking at opportunities to work as a

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consultant.
I think initially I thought it would just be a bridge until I found something else. But I considered two different firms and selected NDA Partners.
Q. And when you were at FDA, obviously, you were in the Washington, D.C., area; right?
A. Yes, that's correct.
Q. Okay. And where -- back in 2004, where was NDA Partners, L.L.C.? Where was their office located?
A. We had a physical office for the business side of things in Virginia, in suburban Virginia. It's now in Madison, Virginia, down near the University of Virginia.
Q. And how many individuals were part of NDA Partners, L.L.C., when you started discussing an opportunity with them?
A. There were ten partners.
Q. Okay. And had you had any sort of dealings with these ten individuals while you were at FDA?
A. Yes. The founder of the group is Carl Peck, and Carl was the director of the Center For Drugs and the person who recruited and hired me at FDA to be the division director for Anti-Viral Drugs.
There were other members that I knew. One of them had actually been on an advisory committee that --

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while I was at -- while I was at FDA, Dr. Lou Scheiner, and while I was at FDA and Dr. Peck had left FDA and he was a faculty at Georgetown, some of his faculty who I met at that point were also partners in this -- had left the university and were parts of this firm. So I knew about half of the -- I knew about half of the partners when I joined them.
Q. Did you voluntarily leave FDA?
A. Yes, I did.
Q. Then from 2006 to 2008 it looks like you went to work for a pharmaceutical company?
A. Yes, that's right. I became an inactive partner. I kept my equity but I became an inactive partner.
Elan allowed me to follow up with my existing clients but I took no new clients during that time. And I -- at Elan Pharmaceuticals I was the senior vice-president for global regulatory, safety, and biostatistics.
Q. And what kind of products does Elan Pharmaceuticals deal in?
A. The company has changed at different points in time, but when I was there, the products that were active were products for neurologic diseases, such as multiple sclerosis, Parkinson's disease, Alzheimer's,

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chronic pain which requires pain pumps into the intrathecal space by the spinal cord.

So it was largely a neurology product, product company, at the time that I worked there. We had a couple of antibiotics but the new products were all in the neurology area.

Q. Any contraceptive products?

A. Not at the time I was there.

Q. Okay. Then 2008 to 2010 -- well, let me back up.

Why did you leave Elan Pharmaceuticals?

A. I was commuting from Phoenix to South San Francisco and my wife had -- was still at the research institute in Phoenix, and so after about a year we made a decision to sort of look for a job where we could both work in the same city. And we looked for something in the Bay area, where I was working, but Amgen in Southern California offered both of us a position, and so I left Elan at that point and both of us went to work for Amgen.

Q. And what did your wife do for Amgen?

A. She's an oncologist. She was director of one of the large divisions at the National Cancer Institute. So she became part of their cancer drug product development team.

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Q. And what kind of products did Amgen sell?

A. Amgen had six or seven products on the market. Most of these were -- the most successful of them were biological products, some of them were growth factors.

I mentioned before that growth factors can stimulate the body to make more white cells, which protects you from infections and cancer.

The erythropoietin was another product that they manufactured that could stimulate the body to make red cells and treat anemia in patients that don't have normal levels of erythropoietin, which is the situation with kidney failure.

They also had products to treat psoriasis, rheumatologic conditions, and, you know, products for cancer, for bone disease.

Those were the six or seven approved products, and then at any given time they typically had about 40 products that were in human clinical trials being evaluated for whether they should progress to more extensive trials.

Q. Any contraceptive products while you were working at Amgen?

A. No, there were not.

Q. And then you left Amgen to go back to NDA Partners in 2010; is that correct?

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A. That's correct.

Q. Why did you leave Amgen?

A. It was a planned departure. I was -- I wanted to actually increase the amount of time I spent teaching, and it was a real challenge for me to teach in Arizona while I was working for Amgen in California and with their schedules. And I also enjoyed the independence of being a consultant.

And so I actually informed the person I reported to that I was planning to leave and he asked me to stay for another six months to recruit and train a successor, and I did that and then left at that point.

Q. Were you ever asked to leave Elan Pharmaceuticals or Amgen?

A. No.

Q. And at Amgen, as the vice-president of global regulatory affairs, what did you do?

A. I was responsible for a team of regulatory affairs professionals.

I had direct responsibility for the U.S. and Canada interactions; I had supervisory and strategic responsibilities for European submissions, although we had a group of regulatory people on the ground in Europe that did the direct work there that was somewhat parallel to my activities; and I also had

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responsibilities for a regulatory policy staff that evaluated FDA guidances and, you know, changing FDA policies and changes even in the law.

Q. Were you involved in preparing NDAs for Amgen?

A. BLAs, yes. These were biologics, so like -- they're like an NDA, except they're biological licenses instead of New Drug Applications.

Q. Okay.

A. But we also did have NDAs as well. We had a product, it would have been supplements that I would have been involved in, but we had a small molecule for bone disorders and kidney disease that I was involved in preparing reports and applications for new indications, designing studies for new indications, post-market surveillance, those types of things.

Q. Were you -- while you worked at Amgen, were you involved in preparing Periodic Safety Update Reports for products?

A. I was responsible for submitting them and seeing -- you know, reviewing them as part of that process.

At Elan, those -- the safety reports and things were my direct responsibility because at Elan I had regulatory and safety.

At Amgen, I was in a much larger company and I

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was responsible for regulatory but I had a role in all of the safety communications and filings and on all the safety committees and so forth but safety itself was directly supervised by another individual.
Q. Were you the signatory on the PSURs?
A. No, I was not.
Q. But you did review the PSURs?
A. Yes.
Q. That was part of your job?
A. Yes, that was part of my job.
Q. And --
A. And at Elan, my job was to organize the staff to prepare them. And I was much more hands on there, although I still was not the signatory, as I recall. I may have been but I don't think I was.
Q. The PSURs I've seen have been, you know, very large. I mean, there are many, many pages.
A. Yes.
Q. Based upon your experience from the pharmaceutical company side, tell me a little bit about, you know, what goes into preparing a PSUR.
A. Sure. Well, you know, it's a very structured document. It has a very specific organization and content.
Some of it I sort of describe as being similar

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to getting a phone book. You can look things up and you know where to find them. You don't have to start at the beginning and start reading to try and find things.
So the PSUR is a -- well, the PSUR is the European format, as you may know. The U.S. requires Periodic Adverse Drug Event Reports, PADERs, and annual reports, quarterly reports initially, then annual reports.
FDA will accept PSUR reports because they're so similar. So, actually, while I was at FDA, FDA agreed and the Europeans agreed that they would accept an annual report and that the annual report would be due on the drug's birthday, actual birthday.
Before that, when I arrived, actually, you almost had an annual report in every region due every couple of months because it was totally unsynchronized and there were different reports.
So anyway, they are different formats, but whether we -- you know, we can call them PSURs or PADERs, whatever you'd like.
One large part of it is to collect the individual spontaneous reports that have occurred and to actually print those and to provide those. Now they're electronic, of course.
Those same reports are actually organized by

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type of condition. So if you were interested in what are the neurologic complications of levonorgestrel, there will be a section where you can actually look and see what types of things have been reported. Headache could be a common one but an IIH a rare one.
And there is a -- sections that -- where you compile the literature. FDA has changed its policy from time to time. There was a period where they said, don't send in the literature when everything was paper because the FDA has access to the National Library of Medicine.
Now, because everything is electronically, the practice varies. But you submit a bibliography of new information, you provide in the annual reports or the periodic safety reports listings of the ongoing studies and there will be a section that describes that.
And there are also are parts of the PSUR where you address specific issues that are being followed. Some of these come from requests from a regulatory body. In Europe, there's actually a formal process for designating certain issues for follow-up.
So the process of putting these together, one year it starts, as soon as you finish one year's report, you start compiling it the next. And then when it's compiled, generally speaking, there's a cover letter that's written by someone in regulatory affairs and it's

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submitted electronically these days, in paper in the old days to the regulatory agencies for their records and their review.
Q. So how -- you know, generally, when you're preparing one of these periodic reports, how much time goes into compiling the information and putting that in the form that the regulatory body wants it in?
A. The compiling is not the whole picture because most of the reports have already been -- like I say, the 15-day reports that may be provided again in the PSUR. The real time of preparing those went into the time when the reports initially came in and the people, the staff, are collecting the information, getting follow-up with the reporter, coding them, entering them into the database.
At the end of the year, when they're all in the database -- and Argus is one of the databases -- then the database is actually designed to actually create the reports either with the MedWatch format or the SIANS format, the European format, and spit them out, if you will, all organized.
So the compiling at the end of the day now is not where all the time is. The time comes in collecting the original information.
But that said, I think when the company puts

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together a PSUR, it also takes that opportunity to make sure that they read it and sort of take a look at the summary at this point in time and say, all right, is there -- are there things in here we haven't noticed before or, you know, does this give us a better insight into something?

So there's -- I can't even begin to estimate the hours. I think our staff that did most of the work at Elan, a small company, was about 16 people but at Amgen, between regulatory and safety, there were over 900 people. And so it's -- there's a lot of -- there's a lot of people that go into that. And then most companies had contractors to help with the post-marketing surveillance.

Q. And so back when you were at Elan and Amgen, is that back in the days you said you'd still send it to FDA in paper form?

A. No. It was electronic by then.

Q. It was?

A. Yeah.

Q. Okay.

A. It's gotten more and more electronic.

You know, in those days we would actually, for example, just to give you a small example, we would actually write out the MedDRA codes, that's the coding

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dictionary for adverse reactions, they actually write them out on the form. Now FDA says submit them electronically and just submit the code, don't submit the text, because the text may change slightly over time. Like, you know, as you know, this syndrome has been called three different things over time but, ideally, the code will always be the same.

Q. Right.

A. So FDA now says, well, just submit it electronically and just submit the code.

So there's -- it gets more and more electronic over time.

Q. Now, when you were back at FDA in 2004, were you guys getting them electronically or in paper back then?

A. We were getting them electronically, although in those days what electronic usually meant was that we would get PDF files, we would get Acrobat files, and some of them in Word documents. If we wanted the ability to edit or cut and paste things from the documents, it's easier to do that in Word than Acrobat PDFs.

Where things evolved since then is that now they're submitted almost like web pages where the information on the reports is tagged the way -- I don't know if you've ever seen what's underneath a web page,

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but it's all plain text but there's a lot of instructions that says, you know, this font, this color, center it --

Q. Right.

A. -- and so forth, or this is the table of contents or this is a new page.

All of that tagging is now embedded so that the reports actually automatically load into the databases, automatically load into the FDA record systems and the European record systems and the Japanese record systems. They've harmonized and standard this -- standardized this and this has been a process that has been evolving.

And FDA calls submitting now publishing. When you submit something, you publish it to the FDA website because it's coming in as a tagged document. Labels are all that way now.

Q. Now, back when you said that it might arrive in PDF form or Word form, was somebody just E-mailing a document to somebody?

A. No. In those days, what you'd get is you'd get the paper for archival records, and some reviewers would actually work off of a paper record when it came in but they would also have the PDF that they could load on their computer. And so you -- a typical application would be the paper submission plus the electronic

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versions.

Q. Okay.

A. And then FDA would load the electronic versions into its electronic document room, but for a long period and I imagine some types of records might -- this still might be true, they kept both the paper and the electronic. And it depended on the reviewers, which they preferred to work with oftentimes in the old days.

There was even a period where every company did something slightly different and they actually sent in the computers but then they sent in the paper for archival purposes.

So it's really evolved over this time period. When I arrived at FDA in '92, we weren't using Windows and we didn't even have E-mail that was the same system-wide. If you wanted to send an E-mail to another floor, you printed it out and somebody put on their sneakers and ran upstairs.

Q. Uh-huh. Uh-huh.

A. It was called sneaker mail.

Q. It's amazing how far we've come along.

A. Yeah. My first job in college was to calculate standard deviations on a manual calculator so...

Q. Well, you know, I've worked on a gubernatorial campaign, a successful one, in 1995 and I tell people we

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had one computer --
A. Yeah.
Q. -- for the entire state. That's amazing.
A. Yeah. You know, in those days, the University of California listed the university's fax machine. It was not plural.
Q. Okay. One other thing. This has been helpful, kind of getting a peek behind the curtain.
A. Yeah.
Q. Today, when somebody is sitting at FDA and one of these periodic reports comes in, what are they seeing on the FDA side? Is it going into a database?
A. It will be, quote, published to FDA, so it will be uploaded electronically and then it goes into an electronic record room. And the record room still has much of the same structure that the paper records have. So the submissions are numbered and they're classified in different, you know, different types and there's a database that has the high-level summary of what each submission is. You can see a little of that on the public sites.
The reviewer can actually pull up any of those documents and then, depending on the types of documents, the reviewer can do a full text search. The documents for the last 15 years have had hyperlinks, so you're in

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the table of contents, you click, you jump to that section.
So there's a lot -- it's a lot easier to navigate this stuff now than it was, but even when it was paper, people could do it because it was so organized.
Q. How is -- over at FDA, you know, based upon your experience, you know, how are people assigned to -- how does one know, an employee know, okay, hey, we've got a PSUR in for this product, that's my task? How do people know that? Are they, people, assigned to specific products or what?
A. Yes, they are.
So drugs which are active have a team assigned to it that will -- in contraception would typically consist of a physician, a pharmacologist, an animal toxicologist, animal pharmacologist, a statistician on an as-needed basis, and a project manager who is responsible for coordinating things on the team. Used to be called consumer safety officers, now they're called project managers.
Q. Has it ever been called a team leader?
A. No. A team leader is within a discipline. So each -- so among the physicians, for example, a typical division might have three medical team leaders or four

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medical team leaders. Each of those team leaders would have -- do their own work. They would have some primary responsibilities but they would supervise -- if it's a physician team leader, they would supervise, say, three other physician reviewers. So each physician has a portfolio of drugs that they're responsible for.
The CSO is the point of contact with the regulatory group in the company. As documents come in every day, the CSOs are informed that there's new documents for drugs they are responsible for.
So for active drugs, a medical officer might be responsible for a dozen very active drugs and 20 sleepy drugs, and some drugs that if anything ever comes in, that -- you know, there are some drugs that FDA is still responsible for that are just barely used anymore. So they have -- their work is sort of prioritized by how active the products are.
But when something new comes in, they learn about it. There is usually a little bit of a lag because even though it's loaded and it's somewhat automatic, it's the CSO's job to identify -- you know, identify the documents.
So when I was division director, actually -- and I think things may be busier these days, but in my day, as I recall, one year, when we looked, we were averaging

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about 70 submissions a day.
And a submission could be as short as a thank-you letter --
Q. Uh-huh.
A. -- for a recent meeting or meeting minutes or it could be a PSUR or it could be a single safety report.
So we had 16 medical officer reviewers and there would be about -- you know, between them, they would have eight or so new documents per day that would be logged in that -- and they would be informed of that and they would sort of keep track of that.
And then the teams would meet and they would go over what's new this week, what's pending, do we have company meetings coming up, are there reports, are there deadlines, are there advisory committees so...
Q. And do these individuals that review these submissions, do they have any other responsibilities in their job other than reviewing submissions?
A. In the new drug divisions, which we're talking about, where Dr. Ross and I both spent our time in the drug center, that is the principal responsibility is to review submissions, but in -- it isn't all just reactive.
There are times when an issue is identified that the staff work on, so they might actually seek a consult

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from the epidemiology group or they may ask the FDA's staff to prepare a report of 15-day reports and then they'll typically ask the company at the same time they do an internal one, because they have slightly different databases in the company than FDA.

They may actually do literature reviews and things but it's almost all -- it almost all does relate to their products. There are other responsibilities, you know, there's training and different kinds of things that they have to do and they have to supervise other people, but it is organized around the submissions that come in.

Q. And when we talk about submissions, are these people part of the teams of people who review New Drug Applications and Investigational New Drug Applications?

A. Yes. In -- there have -- there are places in the FDA where they separate the investigational from the approved and they have separate teams once a product is approved, but in drugs the same team is responsible for the -- everything going on with the product when it's -- whether it's investigational or on the market or sometimes it's a mix. You may have studies for new indications for an old product at the same time it's approved for older indications. So it's one team that has responsibility for that. And yeah.

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Q. I think I'm understanding you. I just want to make sure that I'm clear.

The team members that would be involved in an NDA, for instance, for purposes of continuity, is it that same team that then is responsible for reviewing the periodic reports?

A. Yes. And that's the team that's responsible for maintaining the product's labeling.

So there is a safety and epidemiology group and there's an advertising and promotion group that's separate from the new drug groups. They each have their responsibilities. The epidemiology group puts together the database of the AERS reports as it comes in, they do some of their own safety research, but the same type of information is also going to the team that's responsible for the drug.

Q. Uh-huh.

A. And so they work together.

There are more people in the new drug divisions actually tracking safety than there are people in safety and epidemiology, which have a very small part of it.

The team sees everything. They see the animal work, they see the pharmacology, they see the chemistry and manufacturing, which isn't much of an issue with this product, they see recalls that happen.

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I mean, it's -- the new drug division, it's a bit of a misnomer because it's really the new and the old.

Q. Uh-huh.

A. They have the responsibility for new products on the market and maintaining the labels and making the labeling changes and then the other groups work as consulting groups to them, although many of those groups actually have staff that are virtually embedded in the new drug divisions.

There's typically these days a deputy director for safety in most of the new drug divisions that explicitly interacts with safety staff.

Q. On these teams, how many different New Drug Applications or IND applications would they be dealing with in a year, on average?

A. I would say that, you know, if you look at how many New Drug Applications for novel products that had never been previously approved, the number per year for the whole FDA ranges between 20 products and 40 products. I think one year it hit 50 or 55. But 20 to 40. I think the overall average over all the years is 24, is two dozen.

So those 24 applications are split up among what are now 16 new drug divisions, and so in any new drug

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division there's probably only one or two novel products that's going to be approved for the first time in a given year.

Some areas, you know, are -- get more of them, like the cancer. There's a lot more going on with cancer. So that's with the new ones.

Now, there also are New Drug Applications where there's a capsule version of what was a pill, and that's largely reviewed by the pharmacologists and the chemists, not so much by the medical officer. There's about 50 or 60 of those a year. And then there's the labeling supplements and all of the rest of that type of stuff.

But your average medical officer would probably only deal with a brand-new drug every couple of years but would have applications for new versions of old drugs or new indications or safety updates for probably I would say averaging 8 to 20 drugs at any given time, of which there's probably three or four that are really active and the rest it's more -- you know, there's not as many things going on.

Q. What about generic drugs?

A. That's a whole different division. And those come in by the hundreds.

Q. It's -- but it's part of the CDER, right,

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though?
A. It is. It's its own group. And the generic drugs, you know, do not review labeling at all, they don't review safety at all. They review whether a product is bioequivalent, meaning if you take two versions of the same drug, do you get the same blood levels and is the manufacturing being done to FDA standards. That's the basis for the approval of a generic drug.
Q. Okay. Back to your CV, it looks like you taught a food and drug law class at Arizona State University?
A. Yes.
Q. Is that right?
A. Yes. I still do.
Q. Okay. Yeah. It says 2005 to, nothing is in there so --
A. Yeah. I've done that --
Q. So you've been teaching that for the last 11 years or so?
A. Yeah. Whatever that is. Yeah, 11 or 12.
Q. And is that -- is there a law school at Arizona State?
A. Yes. They're quite proud of it. I know in the East you probably don't even know that there's a university called Arizona State. But it does have a

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good law school and --
Q. Is this course at the law school?
A. Yes. It's an elective course. It's jointly offered to law students and engineering graduate students.
Q. Okay. And tell me a little bit about what you teach in the food and drug law course.
A. We -- it's an elective in both the engineering, College of Engineering and the College of Law.
It's -- what we teach is basically how FDA, as a consumer protection organization, is structured, how it derives its authorities, what types of products it has oversight for, and how it specifically interacts with different types of products.
So we begin the course by presenting some of the historical background on adulteration, which is really what drove a lot of these issues in the 1800s and the early laws in the 1900s and the push for accurate, truth in advertising, if you will.
Q. Uh-huh.
A. So there you get misbranding.
Q. Uh-huh.
A. So we talk about those as being sort of the core around -- authorities around which the FDA consumer protections are built and then we spend several weeks on

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each product type.
So we'll talk how are drugs developed, what are the rules for investigational drugs, what's the logic for how they're done, how do the regulations actually shape the science, the studies that are done.
And then we do the same thing with biologics and with devices and combination products, and we talk about how much of FDA's regulation revolves around rules around labeling, which is, you know, in law speak, speech.
Q. Uh-huh.
A. And that's actually FDA's probably principal tool is regulating speech. And we talk about -- there's been a lot of developments and controversies over the years of how speech is regulated by consumer protection agencies.
And so we present that sort of framework, talk about FDA's enforcement authorities, we talk about manufacturing standards for different types of products, we take a brief look at how other countries organize their, you know, their efforts, some similar, some not so similar. We look at how FDA gets involved when there's a public health crisis like a new epidemic or something like that so -- and what does FDA do to encourage development of products where there's unmet

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medical need.
So there's 13 two-hour lectures in the course and the principal teachers for the last ten years have been myself and a pharmacist/lawyer. And so we have kind of complementary backgrounds. He teaches the engineers a little bit about torts and to give them some background and we talk about how preemption is a factor in that.
The course is really more a health policy course than a law school course, per se. It's not taught like a case law law course.
Q. Uh-huh.
A. It's really more kind of a blend of health policy.
There are two very different groups of students. Some of them know a lot of science and the other of them know a lot of law and then they see kind of how the two merge together.
Q. Do you use a textbook in this course?
A. We have. We've used a textbook by Adams that's published by the Food Drug Law Institute on FDA.
Frankly, we found it was too much law and not enough of the science background so we largely teach the course based on FDA documents and public documents and when a topical issue arises, you know, such as

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compounding, for example, we'll even pull in the press stories and the Center for Disease Control documents and things.

So we have a tool called Blackboard, which wasn't around in my day when I was a student, but it allows the students to actually have access to reading materials. And so we have them read sections of the law and sections of regulations and the guidances that all fit together and then we usually try and find some topical news stories and things to kind of put some flesh on the bones.

Q. Other than the Adams textbook, have you ever used any other textbooks?

A. No. Some of the students follow Peter Barton Hutt's book. He's got a case law, case law book.

I taught an undergraduate version of the course for a couple of years and we used, I think his name is Hilt, but there was a book written with kind of more of a lay perspective that we used when we taught it with undergraduates. And we didn't -- we didn't cover much law.

That one really was looking at sort of just the whole system and how the Government sets up administrative agencies that have responsibilities that are delegated to it by Congress and how that all works.

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Q. And you mentioned your lawyer/pharmacist that --

A. Yes.

Q. -- co-instructs with you.

What's his or her name?

A. His name is Roger Morris. He's at Quarles. So he's another volunteer faculty like myself.

Q. And you mentioned that he kind of provides the insight on the tort law.

A. Well, he does -- he's the lawyer of the two of us, so if it's something that has to be framed in the way that lawyers think about things, he does that part of the lecturing, I bring the medical, the FDA, the policy, the regulatory sides of things. So we complement each other pretty much.

Q. And in this course do you teach or discuss the difference between common law and FDA regulations?

A. Very, very lightly. We sort of talk about the fact that there are these different -- particularly for the engineers. The law students probably know this. But we talk about how there are different ways that the law comes about. Common law is one, legislation that specifies certain things interacts with common law but -- and then there's administrative law, which is kind of an interesting body unto itself.

But that's probably a more advanced topic. This

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is really -- you know, could be nicknamed FDA-101. It's similar to the courses that companies offer their employees that are getting into regulatory except that we do more deliberately sort of focus on the fact that the law gives FDA certain authorities and then they have to actually find ways to use those authorities to get what they want done and how they -- and the rule-making process and the transparency, which is unique in this country compared to many other countries.

Q. And you mentioned preemption before, which is a legal concept.

A. Yes.

Q. And do you -- have you guys taught in this class about, have you heard of a case called Wyeth v. Levine?

A. Yes. And Mensing and other things.

You know, in 2005 preemption was one of our more boring topics. It's gotten progressively more interesting over the years, probably more to the faculty than to the students.

So we introduce, we introduce the concept that there are times when the federal law preempts state laws.

Q. Uh-huh.

A. And we don't really offer opinions about it, we just really say this is -- these are the developments,

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these are -- this has been how it's been applied --

Q. Uh-huh.

A. -- and, you know, talk about some of the ways that that influences consumers' ability to, you know, seek remedies through the tort system as opposed to some other mechanism. So, yeah, it's been an interesting, it's an interesting area.

Q. And you understand that in Wyeth v. Levine the Supreme Court has said the manufacturer is responsible for its label; correct?

A. Yes. And I don't think FDA would have ever disagreed with that. It's that's who is responsible. They're also responsible to comply with the labeling requirements of the Food, Drug and Cosmetic Act. But it is their label. They're -- you know, I think I've said in testimony that the buck stops with the company when it comes to the label.

Q. Uh-huh.

MR. JONES: I have 12:26. Do you want to go for lunch now?

MR. SCHMIDT: Sure.

MR. JONES: I mean, this is a good breaking point.

MR. SCHMIDT: Sure.

MR. JONES: All right. Let's go off for lunch.

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VIDEO OPERATOR: We are going off the record. The time is 12:26.
(Luncheon recess, 12:26-1:21 p.m.)
AFTERNOON SESSION
VIDEO OPERATOR: We are back on the record. The time is 1:21 p.m.
BY MR. JONES:
Q. Dr. Feigal, welcome back. I hope you had a nice lunch.
A. Yes. Thank you.
Q. FDA regulations have the same binding force as the law itself; correct?
A. Generally speaking, yes, that's true.
Q. Okay. And failure of a product to meet these standards is a violation of the law; correct?
A. It can be, yes.
Q. And do you agree that not all adverse effects can be anticipated during clinical trials?
A. Yes.
Q. Let's talk about, what's an Investigational New Drug Application?
A. That is an application for FDA to seek permission to conduct studies in humans for a drug which is not approved for marketing in the United States.
Q. And was there an IND submitted for Mirena?

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A. Yes, there was.
Q. And who submitted the IND for Mirena?
A. You won't mind if I refer to my report.
But the initial IND was filed in 1983 by the Population Council, which is a non-profit organization that has developed some contraceptives over the years.
Q. What do you know about the Population Council other than that?
A. I've had a little bit of contact with them over the years. I co-served as the head of an antimicrobial contraceptive task force with someone from the Population Council when I was in anti-viral drugs, but my understanding is it's a non-profit organization that helps develop contraceptive alternatives for women.
Q. Who have you worked with from the Population Council?
A. You know, I've forgotten his name over the years.
Q. Did you -- are you aware that the Population Council developed the Norplant implant device?
A. I may have known that. I don't recall if I knew that or not.
Q. Did you know that the Population Council had developed the copper IUD ParaGard?
A. No. I may have known that. I don't remember

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which -- other than the morning-after pill, I'm not sure if I remember any other specific. But I know that they have been developing contraceptives for many years.
Q. And did you review the Mirena IND before preparing your report in this case?
A. I did review selected summary documents that described the IND and the early development when I prepared my first report for Mirena last year.
Q. How many pages is that IND?
A. I don't know.
Q. You reviewed the summary reports contained within the IND?
A. No. What I reviewed is some of the key documents from the NDA which describe the entire IND process and the studies that were conducted under that IND.
Q. Okay. So you did not review the actual IND?
A. I don't recall if I had access to the actual IND, but I had the descriptions at the time of the approval of the product in the NDA documents.
Q. Okay. And what is an NDA?
A. NDA is a New Drug Application. So that's an application if it's an initial IND for the first authorization to market a drug in the United States.
Q. Okay. And it's the drug product's sponsor that

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submits to FDA an NDA containing the data that it has gathered on the product's safety and effectiveness; is that correct?
A. Yes, that's part of what's in an NDA.
Q. What else is in an NDA?
A. Well, there are extensive records about the manufacturing, there are animal studies that are used for a variety of different kinds of purposes, there are summaries of the clinical trials individually both with respect to the effectiveness and the safety of the product.
The various sections are organized into -- organized and described in different summaries, the important ones for safety and effectiveness or the Integrated Summary of Safety and the Integrated Summary of Effectiveness.
And then the NDA also contains listings of the original data that the patient, or if it's an animal study at the animal level, and often contains -- and today always contains data sets of that data for the FDA statisticians to evaluate.
Q. That sounds like a lot of data.
A. They are. They're big applications.
Q. Okay. And did you review the NDA for Mirena?
A. I reviewed some of the summary documents that

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described the relevant portions of the NDA for my opinions.
Q. Other than the summary documents, did you review the rest of the NDA?
A. All of the different sections? No, I did not.
Q. Do you know how many pages the Mirena NDA was?
A. I do not.
Q. Do you know how many volumes the Mirena NDA was?
A. No, not sitting here, I don't.
Q. Do you -- can you approximate how many pages would comprise the original Mirena NDA?
A. No, I really don't have a way to do that because I don't know the types of individual data that -- the bulkiest part of the NDAs are the so-called raw data, the individual data, but at this time period, in 2000, it still wouldn't have contained all of the case reports for them. So I just don't have enough information to be able to estimate what -- you know, what -- how many volumes or the size of the application.
Q. Do you agree that the ultimate purpose of the review of the preclinical and clinical data contained within the NDA is for FDA to review and ultimately approve the product with a label that provides adequate instructions for the safe and effective use of the drug for the purposes indicated?

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A. Long, long question.
Generally speaking, that is correct. There's a part of the statute that actually does refer to adequate instructions for use but that pertains to over-the-counter drugs. But FDA's understanding of what adequate instructions for use for a prescription product is found in the prescription drug labeling sections, 201 and 202.
Q. When a product is -- when a New Drug Application is submitted, it is based, in part, upon preclinical and clinical studies conducted by the product sponsor; correct?
A. Yes, that's correct.
Q. FDA doesn't do any of its own independent, individual studies; correct?
A. That's almost always true. FDA does not do the clinical studies or the animal studies. The sponsor does those and then FDA reviews the data and inspects those studies.
Q. In this case, FDA did not do any sort of independent studies on Mirena before it was approved; correct?
A. Not to my knowledge.
Q. Now, the contents of a label, they're initially the result of discussions between the sponsor and the

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FDA; correct?
A. Yes.
Q. And I think you described it in your report as a negotiation; is that correct?
A. I may have used that word. It's -- you know, "discussion" is also a good word.
A label consists of a concise summary of scientific evidence, and there is some discussion between the manufacturer and the FDA on the best way to summarize the information that's available.
Q. But you used the word "negotiation" in your report; right?
A. I don't recall if I did. But it's -- but I would agree that it's not negotiation in the business sense of trading this for that, it's really more of a discussion of trying to develop a consensus, a consensus on what is an adequate description, what is an adequate summary of the scientific evidence on which the approval is based.
Q. Now, you say in your report at Page 5 that Phase 1 trials are small, closely monitored studies, usually in normal volunteers, to learn how a drug is absorbed and eliminated from the body and to determine doses for further testing; is that correct?
A. Yes.

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Q. Okay. And you say, typically, fewer than a hundred subjects participate in Phase 1 trials; is that correct?
A. Yes, for most drugs that's typical.
Q. Do you know how many subjects participated in the Mirena Phase 1 trials?
A. I don't know if -- I don't know if I described that. I really described Mirena from the standpoint of the evidence that was available at the time of its -- time of its approval, and I do have the numbers of the total number of patients studied from all the different phases and in the pivotal trials but I don't know if I broke out the Phase 1 trials separately.
Q. Okay. And you say, Phase 2 trials are the first trials to evaluate the effectiveness of the drug for patients with a particular condition. These studies often involve several hundred patients.
Is that correct?
A. Yes, that's correct.
Q. And it says, they are used to learn enough about the drug to plan for larger trials in Phase 3 that will study the safety and effectiveness of the drug for one or more indications; is that correct?
A. Yes, that's correct.
Q. And do you have any idea as we sit here today

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how many subjects were involved in Mirena Phase 2 trials?
A. No, I didn't break it out that way. I think what I summarized is that the application contained 20 clinical trials and was based on total study of 3,021 patients.
Q. Okay. And then you say that the purpose of Phase 3 trials is to study the safety and effectiveness of the drug for one or more indications; correct?
A. Yes, that's correct.
Q. And what indication was studied in the Mirena Phase 3 trials?
A. It was its indication as a contraceptive, to prevent pregnancy.
Q. It was not studied at that time for heavy menstrual bleeding?
A. Eventually, that is another indication that was sought. I don't recall the timing. As I recall, that was an indication which was obtained later.
Q. Okay. And just so we're clear, so at the time Mirena was approved it was approved for contraception, not for the treatment of heavy menstrual bleeding; correct?
A. I believe that's correct. I might need to review the history. I focused on the initial approval

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and not on the subsequent approvals in my report.
Q. And did you say something about you thought there were about 20 trials that preceded the Mirena approval?
A. Yes.
Q. Then you mentioned something about pivotal trials?
A. Yes.
Q. And what are pivotal trials?
A. Pivotal trials are usually the subset of trials that form the basis for the evidence of effectiveness.
Safety is based on all the clinical trials but effectiveness usually relies on one or more clinical trials, Phase 3 clinical trials, that demonstrates effectiveness.
Q. So if I'm understanding you correctly, the safety of the product and the warnings that are ultimately included in the product's labeling are determined from the company's experience in the 20 clinical trials that preceded approval.
A. Yes. It would be their experience in -- it would be their entire -- the safety would be based on their entire body of studies.
Since this was a product that was marketed outside the United States, it would also -- the safety

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evaluation at the time of the NDA approval would also include evaluation of the marketing safety experience in Europe, for example, as well.
Q. And how many subjects did you say were participants in the Mirena pre-approval trials?
A. The safety -- the FDA's Integrated Summary or the company's Integrated Summary of Safety described safety based on 3,021 women in 20 clinical trials, 2,899 for women from contraceptive studies, with the remainder being for studies of menorrhagia or endometrial protection.
Q. And are you sure that that 3,021 number doesn't come from the pivotal trials versus the 20 trials that you've discussed a moment ago?
A. Yes. I describe -- in my report in the section on effectiveness I describe the pivotal trials, and the summary of effectiveness describes 17 trials of the 20 and they also described that the trials included 1,594 women from qualified sites, sites which where the clinical trial standards met the same standards that a U.S. study would meet.
Q. Mirena is indicated for usage for a five-year period; correct?
A. Yes.
Q. And how many of these 3,021 women were studied

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for a full five years?
A. I'm not sure I noted that in my report, except for effectiveness. Among the effectiveness patients, there were 633 women of the 1,594 that completed five years of study.
Q. So this five-year product was approved based upon a study containing only 633 women who used the product for five years; is that correct?
A. Yes, that's correct. It was a study of, you know, close to 1,600 women but only 633 had used the product for five years.
Q. How many used the product for just one year or less?
A. I didn't break that out in my report. I would have to go back to the document to look that up.
Q. How many were -- of these women used the product for two years or less?
A. Again, I didn't look -- I didn't break that out. I presented representative summary statistics of, you know, the description of the effectiveness. So that information I'm certain would be in the reports but I'd have to go back to the reports to look for that information.
Q. What reports are you talking about?
A. Well, the source I relied on is the Integrated

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Summary of Safety, which summarizes all of the studies, rather than trying to compile the data from the individual studies myself.
Q. How many of these women were studied in the United States?
A. As I understand it, the majority of them were not, that these were the studies that had been conducted in Europe, where it was first approved.
Q. How many of these women -- strike that.
Are you aware that certain study data was excluded from full analysis because the studies were conducted at unqualified sites?
A. Yes. I mean, I described the fact that the pivotal trials were based on qualified sites that met certain criteria, that met U.S. standards. There were other sites that, for different reasons, were not considered, were not relied on for the effectiveness because, one reason or another, that they didn't meet U.S. standard for trials.
Q. Do you believe a pharmaceutical product should be approved based upon less-than-perfect data?
A. Well, I think you always have less-than-perfect data. It's a matter of judgment as to whether or not the data is adequate to describe the effectiveness.
And the criteria for whether a site was

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qualified or not, as I understand it, was criteria that FDA worked out with the company.
Q. Does goodwill with the regulators ever come into play in the product approval process?
A. Well, I mean, I think companies do strive to have a good relationship with FDA but I don't think FDA tries to factor in whether there is goodwill or some other kind of ill will with a company. They try and look objectively at the information that's in the application.
Q. Do friendships between government regulators and pharmaceutical companies develop from time to time?
MR. SCHMIDT: Objection. Vague.
THE WITNESS: I mean, there's a lot of people in -- on both sides of the table. I'm certain that there probably are friendships and that there are many relationships who are -- they're cordial working relationships.
(Exhibit Feigal-6 was marked for identification.)
MR. SCHMIDT: What number are we at?
THE COURT REPORTER: Six.
BY MR. JONES:
Q. Dr. Feigal, I've handed you an E-mail that we're marking as Deposition Number 6.

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A. Yes.
Q. And I want to refer you to the E-mail towards the bottom from Dr. Bettina Fiedler.
And this E-mail is talking about getting approval in another country. And Miss Fiedler, can you read what she says starting at "However" there in the middle of the paragraph?
A. However, you should be aware that the Berlex regulatory affairs is currently going through a major reorganization.
Q. All right. No. The other "however" above that. Here. You can see on the ELMO.
A. Oh, up there. I'm sorry. There are several howevers on this page.
Q. Yeah.
A. However, with regard to the U.S. submission of Mirena, you should be aware of one big difference to your situation in Japan. The FDA is highly interested in getting the product onto the U.S. market, therefore, they worked intensively with Berlex and Leiras to be able to accept data that were not always so perfect.
Q. Keep going.
A. So the Berlex approach of the submission may not be so helpful to you because it was based on some goodwill from the authority, which I'm afraid the

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MHLW -- that's the Japanese FDA -- may not have towards a fertility-control product.
Q. Okay. Did you know, based upon your review of the documents that you were provided in this case, that the FDA was highly interested in getting the product onto the market in the U.S.?
A. Well, this isn't the FDA speaking, but FDA, in general, is highly interested in seeing that new, safe and effective products come on the market. It's not an adversarial relationship.
Q. Did you know from your review of the documents that you were provided in this case that Bayer felt that the FDA had worked intensively with Berlex and Leiras to be able to accept the data that were not always so perfect? Did you know that?
A. Well, I was aware of the fact that FDA carefully developed criteria for identifying clinical trials where the sites met the U.S. standard and then didn't consider the other sites' data for effectiveness, and so I imagine that was a process where they had to work closely together and intensely to see if there was something that -- in those trials that could be used for an approval decision.
Q. Do you agree that the data submitted for the approval of the Mirena product were not always so

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perfect?
A. I don't know what this person meant, but if it's simply commenting on the fact that some of the sites, looking back over studies done over the past ten years, didn't meet the standards for clinical trials at the time of the approval, it may simply be referring to the fact that there would be sites that would be relied on and other sites which wouldn't be considered for effectiveness.
Q. Did you know, based upon your review of the documents provided to you, that Bayer felt that the approval of Mirena was based on some goodwill from the authority, meaning the FDA?
A. I'm -- I don't think it was based on goodwill. I think it was based on the evidence, which is well laid out in the summary documents.
I think the author here is commenting on the country differences. As I understand, Japan has been very reluctant to approve hormonal contraceptives, and condoms are the major form of contraception in Japan, unlike this country.
So I think they're commenting on the fact that the environment is different, going to a regulatory body that approves hormonal contraceptives in many different forms compared to a country that relies on barrier

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contraceptive methods.
Q. So are you disagreeing with Bettina Fiedler, the global regulatory affairs employee for the company, when he or she says that the approval was based on some goodwill from the authority?
MR. SCHMIDT: Object to characterization, foundation.
THE WITNESS: Well, I think she's describing -- I mean, I don't know what she meant. I don't. I don't know what she meant by that, but what she's describing is the fact that there was data that wasn't relied on. That's the data that's less than perfect. That's part of the record of the approval process.
If that's what she means by goodwill, then I would agree that FDA was willing to accept historical studies and to identify the subset of studies that met FDA's current standards.
FDA could have taken a hard position and just said, do the studies, do new studies and start over, but they worked with the company to see if there were studies that met the standards, found those studies, and made a decision based on them.
BY MR. JONES:
Q. Based upon some goodwill from the authority --
A. No. I don't think --

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Q. -- according to Miss Fiedler.
A. Well, I don't know what she means by goodwill, but you can see that FDA did work with the company to identify the subset of studies that they wished to consider that they considered met FDA standards for adequate and well-controlled trials to be the basis for the effectiveness.
Q. And just to be clear, you've never seen this document before today; correct?
A. Not that I recall.
Q. It's not something that Bayer's lawyers provided to you; correct?
A. If they do, I don't recall having seen it.
MR. JONES: And just for the record, we'll note that that's Bates numbered MIR_PSEU_00546368.
BY MR. JONES:
Q. Down towards the bottom of Page 6 of your report you say, FDA employs a number of resources in reviewing the NDA data, including a team of physicians and other scientists who are experts in their respective fields. This team prepares detailed reports in their area of expertise based on their findings.
Are these the summary reports that you've mentioned you reviewed earlier?
A. No. The documents that I'm -- the ISS and the

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ISE are actually the company documents.
FDA has reviews of those documents, and I read those as well, but I -- for the description of what was in the ANDA, I took that from the company's summaries.
Q. Okay. It says, these reviews and reports may contain conclusions and recommendations of the individual reviewers at the time they are written but do not necessarily represent the final FDA position; is that correct?
A. Yes, that's correct.
Q. Your next sentence you say, during the review process, FDA has complete access to all of the data from the studies in the NDA either as submitted at the time of filing or per FDA's request to the NDA applicant.
Did I read that correctly?
A. Yes.
Q. Do you know, based upon your review of the documents in this case, whether FDA had complete access to all of the data from the studies in the NDA or whether they had requested it at some point?
A. Well, there certainly were both. I think that I described that during the NDA, the company submitted 41 supplements.
So supplements typically contain additional information or analyses or data that FDA requests. So

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there's, you know, evidence that it was a very interactive process, that FDA used not only the NDA but requested additional information and it was submitted 41 different times.
Q. Did FDA have access to the case reporting forms from the studies that were listed in the NDA?
A. I would -- I don't know. I don't know directly which case reports. There are always some case reports that are included but I don't know if this application had all case reports.
Q. And when I say "case reports," I'm talking about the case report forms.
You know what that is; right?
A. Yes. Right. The raw data from the individual --
Q. Right.
A. -- trial participants. Yes.
Q. Does FDA engage in a risk/benefit assessment during its new drug approval process?
A. Yes.
Q. Okay. And I believe you said that this risk/benefit assessment is conducted with every FDA approved on the market and is a crucial element of the drug approval process; is that correct?
A. Yes.

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Q. And so we're talking about Mirena, a contraceptive; right?
A. Yes.
Q. Okay. Were there other contraceptives on the market at the time Mirena was approved?
A. Yes.
Q. There were oral contraceptives; right?
A. Yes.
Q. Norplant was still on the market in the U.S. at that time; correct?
MR. SCHMIDT: Bless you.
THE WITNESS: I don't recall the year Norplant was withdrawn but --
BY MR. JONES:
Q. If you don't know, that's fine.
A. Yeah.
Q. ParaGard, the copper IUD, that was on the market at the time; right?
A. There were copper IUDs on the market at the time, yes.
Q. Copper IUDs have been on the market in the U.S. since the 1980s; right?
A. Yes.
Q. And a copper IUD is a non-hormonal IUD; right?
A. That's correct. I think there were -- I think

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the Copper T was actually on the market in the 1970s.
Q. And the Mirena, that's a hormonal IUD; right?
A. That's correct.
Q. And it releases a potent synthetic progestin called levonorgestrel; correct?
A. That's correct.
Q. And do you agree that there is systemic circulation of levonorgestrel in Mirena users?
A. Yes.
Q. And you agree that Mirena users experience systemic hormonal effects as a result of their use of the IUD; correct?
MR. SCHMIDT: Objection. Characterization.
THE WITNESS: They can. There may be systemic effects. It does circulate systemically, yes.
BY MR. JONES:
Q. This process of the risk/benefit assessment, that continues to occur throughout the life of the drug; correct?
A. Yes, that's correct.
Q. As the company receives reports of adverse effects, they are to continue balancing the risks versus the benefits; correct?
A. Yes, that's correct.
Q. And do you agree that once a drug is on the

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market, the number of patients who take the drug expands from a few hundred or a few thousand patients in the clinical trials to tens of thousands or even millions of patients who are prescribed the drug?
A. Yes. I think I've written that or something similar to it in my report.
Q. I think that's straight from your report.
And do you -- I think we talked earlier about all adverse effects can't be expected to be picked up in pre-approval trials; correct?
A. That's correct.
Q. Okay. And so isn't it true that there's a period of time as a drug develops more users and more usage that new adverse effects may come to the attention of the manufacturer?
A. Yes, that's correct.
Q. And those manufacturers are supposed to receive that information and determine whether or not an update to their label is necessary; correct?
A. Yes, that's correct.
Q. And at all times while their product is on the market, a drug manufacturer is responsible ultimately for its label; correct?
A. That is correct.
Q. And when you're talking about premarket studies,

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isn't it true that this testing is conducted in a limited number of patients; correct?
A. Well, relative to the eventual use, that is correct. Sometimes it's a very large number of patients, but compared to the use once the product is approved, it is limited, yes.
Q. Okay. And these premarket studies are conducted on a population that's relatively healthy; correct?
MR. SCHMIDT: Object to characterization.
THE WITNESS: Generally speaking. Not always. But for a product to be used by healthy people, it certainly would be conducted in healthy people, yes.
BY MR. JONES:
Q. Well, isn't it true that many of these studies actually have exclusion factors where they keep people out that have certain health conditions?
A. Yes, that's correct.
Q. And they have inclusion factors where they bring in individuals to study that they would like to study in a product; correct?
A. Yes, that's generally true. It varies from product to product and who the target users are. But it is true that the studies try to remove some of the sources of variation, variability, such as patients who have other conditions going on that complicate the

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interpretation of the studies.
Q. Do you know what percentage of women studied in the premarket studies for Mirena would be classified as overweight or obese?
A. I don't think I know that. I don't think I know that number.
Q. Would you agree that it's a relatively small percentage of the women studied?
MR. SCHMIDT: Objection. Foundation.
THE WITNESS: I don't think I know one way or the other. It depends on the setting where the studies are being conducted, and rates of obesity vary in different populations and different ages and with socioeconomic status, so I just don't know one way or the other.
BY MR. JONES:
Q. What is post-marketing surveillance?
A. It's a required activity of companies with products on the market, where they collect information about the reports of potential adverse reactions and look for other ways that -- to identify safety information.
Q. And this information includes spontaneous reports from -- of individual cases from health-care practitioners; right?

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A. Yes, it does.
Q. Patients?
A. Patients? Yes. It -- patients do directly report both to the company and to the FDA.
Q. Okay. The name Foreign Adverse Experience Reports, are those part of the post-marketing surveillance?
A. Yes. The company is responsible for analyzing all of those. The FDA actually identifies which types of foreign information it would like to have submitted and in different settings. So there are slightly different rules for foreign reports than U.S. reports but the company's responsibility is to know about it all and then there's rules about which ones get submitted to FDA and how.
Q. They're supposed to know about all of the information that's out there?
A. No matter how they learn of it, the company is responsible to know about the safety information for their product, whether it's from patients, foreign, from health-care providers or even from lawsuits.
Q. Right. Clinical trials?
A. From clinical trials.
Q. Information from the medical literature?
A. Yes.

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Q. You mentioned lawyers and lawsuits; right?
A. Yes.
Q. And is -- do you put less credence in a report of an adverse event that is learned from a lawyer versus someone else?
A. No. The credence of the report should be based on the content of the report, not who reported it.
So there are reports that are incomplete and difficult to interpret that come from lawyers and ones that come from doctors and so forth. So you judge each report in terms of what you know about it.
There may be limitations in getting follow-up information when there's lawsuits involved but -- compared to a report from a patient or a doctor but the credibility of the report depends on the quality of the report.
Q. Well, as it relates to lawyers and the follow-up, isn't it true that it might actually result in more information because the lawyers can provide copies of their client's medical records?
A. It can. It -- the way that the privacy laws allow post-market surveillance where the patient doesn't give their consent to have their medical history shared with a drug company, which I think would surprise a certain number of patients, but the context for that is

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that the company may seek follow-up from the party that reports the problem but they are not allowed to contact anybody else who they may know of who might have more information. They always have to work with the reporter.

So it will -- reporters vary, no matter who they are, in terms of their ability or willingness to provide additional information.

Q. Can the FDA ask the individual reporter for permission to contact his or her health-care providers?

A. Well, could they is an interesting question.

It's not part of the practice because the privacy laws, which are, have the nickname of HIPAA, actually have a very specific description of how you can get information for a post-market report and it limits it to seeking information from the reporter.

I think that FDA or the company can always request that a reporter could ask other people to contact FDA and to become a reporter themselves but there are certain rules about how this is done.

And then other countries have rules, some of them even much stricter than the U.S., about privacy. In some countries, doctors are not allowed to actually report to the companies, they have to report to the government. So it just varies on who the report is

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from, the circumstances.

Q. With all due respect because you worked at the FDA, that seems silly to me. It seems like it ties the FDA's hands a little bit.

Is that a fair characterization?

A. Well --

MR. SCHMIDT: Object to form.

THE WITNESS: No, I don't think so. I think that -- I think what it is is it -- and, you know, it's not part of the -- it's not part of FDA's law, it's part of HIPAA, it's part of the health privacy laws that are part of HIPAA, is that it balances the public health need for reports with the patient's need for privacy.

BY MR. JONES:

Q. Now, a pharmaceutical company, when they receive a report from a consumer, are they also limited only to talking with the consumer about the report?

A. No. To the reporter. So if it's a consumer, they can talk to the patient, if that's the reporter.

Q. Right.

A. If it's a doctor, they can only talk to that doctor and they can only request additional information from that doctor. And that doctor has no limitations on what they can provide, it's just they have to -- they're the only person the company, under the rules, can ask

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for more information in post-market surveillance.

Q. Could a pharmaceutical company ask a patient for a HIPAA release to talk to his or her other doctors?

A. That's probably a legal question that I just, I don't know the -- I don't know the answer.

One, I don't offer legal opinions as an expert. But I think that's a legal issue around what is permissible and whether or not that would be something that's trying to subvert the privacy balance that's built into HIPAA.

Q. Maybe that would be a good topic for your food and drug law class.

A. It is an interesting topic.

Q. Serious and unexpected adverse events must be reported within 15 days of receipt by the manufacturer; correct?

A. That's correct.

Q. And those are known commonly as 15-day reports?

A. Yes.

Q. And do you agree that the purpose of spontaneous reporting systems is to detect a signal of a previously unknown potential association between an adverse effect and a drug?

A. Yes.

Q. And beyond examining individual spontaneous

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reports, signal evaluation may include epidemiological studies, research on the pathophysiology of the adverse reaction and, where feasible, clinical trials; correct?

A. Yes, those are all things you can do. Yes.

Q. And another important source of safety information comes from clinical trials and other studies conducted after the initial market approval; correct?

A. Yes, that's correct.

Q. And even Phase 4 studies or post-marketing commitments.

A. Yes, that's correct.

Q. Now, in addition to clinical trials, there may also be publications of individual patients or series of patients thought to have had adverse experiences from a drug or from related drugs; correct?

A. Yes, that's correct.

Q. And do you agree that it's well known and understood that additional information about the benefits and risks of medicines will become available after they're approved and that the evaluation of that information is an ongoing process?

A. Yes.

Q. Now, you talk about hierarchy of evidence, of scientific evidence; right?

A. Yes.

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Q. There is a recognized hierarchy of scientific evidence relevant to the assessment of drug safety; right?
A. Yes.
Q. And while it may be at the bottom, spontaneous reports are part of that hierarchy of evidence; correct?
A. Yes, they play a role, particularly in providing a signal and identifying a safety, potential safety issue that needs follow-up.
Q. And would you agree that infrequent or rare adverse reactions are often described initially by individual case reports either reported to the company or FDA or published in medical literature as a case series after the product enters the market?
A. Yes, I would agree with that.
Q. And you agree that a PTC is a rare event; correct?
A. Yes, it is.
Q. Do you agree that, when performed properly, case-control studies are the best method to determine whether there's an increased risk of infrequent adverse events associated with a drug?
A. Yes, when well conducted, when well performed, they are one of the better sources of information about rare events.

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Q. And when both the drug use is infrequent and the adverse event is rare, the very large pharmacoepidemiology databases may be the only practical method to assess the risk; correct?
A. Yes, that's correct.
Q. And are you aware of private companies that provide access to information from regulatory adverse event databases like FDA and WHO?
A. Yes, there are open source, if you will. I'm not quite sure of the -- who -- the structure of all of the organizations that provide them, but there are open-source tools for searching regulatory databases and adverse experience databases.
Q. Well, let me make sure that we're talking about the same thing.
I understand that there are companies out there that will sell subscriptions that a company can buy that would allow them to, basically, search FDA adverse event data; is that correct?
A. Yes, there are. The FDA makes the data available publicly, you know, on a quarterly basis, and so many companies construct their own databases, but they may choose to use the services of a contractor.
Q. They don't make it real easy to see the information, do they?

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MR. SCHMIDT: Object to characterization.
THE WITNESS: The downloadable forms are deconstructed, if you will. You have to put it back together yourself. And they're very large and they're cumbersome and it's challenging to set it up right to get the information that you want. But it is relatively straightforward but there's -- it's tedious, at best.
MR. JONES: Yeah. I actually, point of interest, I had a -- I hired a software developer to build me a database --
THE WITNESS: Uh-huh.
MR. JONES: -- so I could look at it.
THE WITNESS: Yeah. Well, you know firsthand that the definitions change for the fields, the fields move --
MR. JONES: Uh-huh.
THE WITNESS: -- and there are other challenges as well.
BY MR. JONES:
Q. Now, you mentioned that some companies will construct their own databases to be able to review the FDA adverse event information; is that correct?
A. Yes.
Q. Did any of the companies that you worked at have such a database?

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A. No, neither Elan nor Amgen had such a database.
Q. Do you know whether Bayer has such a database?
A. I do not.
Generally, when you're dealing with your own products, you use your own database, and I don't know if they also -- I didn't see anything that indicated that they had an in-house copy of the AERS, now called FAERS, database.
Q. Do you know if they have a subscription to be able to search through the FDA database?
A. I don't know.
Q. You mentioned earlier something along the lines of a company as part of their post-marketing surveillance should be looking for anything that's out there that relates to the safety of their product.
Do you remember talking about that?
A. Yes.
Q. Okay. And would that include looking at the FAERS database?
A. It could. It depends on the -- it depends on the product and depends on the reporting patterns.
90 percent of the reports, on average, that are in FAERS have come from the companies who are responsible for the products. So, generally speaking, the company databases are pretty complete, plus they

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have reports which FDA does not request as part of FAERS. So the company database is typically larger than the FAERS database, although there's always something in FAERS that may not -- the company may not have.
Q. Did you know that in this case that Bayer didn't look at the FAERS database regarding Mirena and PTC until 2015?
MR. SCHMIDT: Object to characterization.
THE WITNESS: I'm not -- no, I don't know if I know when they first looked at it. No.
BY MR. JONES:
Q. Did you know that when Bayer looked at the FAERS database in 2015, that they actually found cases in FAERS that were not part of their database?
A. I don't recall if I knew that, but I would expect that to be the case. There would always be a small percentage of reports that went directly to FDA.
Q. Did you know that it was not part of their, of Bayer's pharmacovigilance practices prior to 2015 to review the FAERS database?
MR. SCHMIDT: Object to form and foundation.
THE WITNESS: I don't. No, I don't think I've seen any company SOPs about what their standard practices were.
MR. JONES: Yeah, I was going to ask you that.

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You jumped ahead of me.
BY MR. JONES:
Q. Have you reviewed any of Bayer's pharmacovigilance standard operating procedures, or SOPs?
A. No, I have not. I have reviewed the analyses themselves but not the SOPs.
Q. The SOPs weren't provided to you by Bayer's lawyers?
A. No. And I didn't request them.
Q. When you're evaluating whether or not a pharmacovigilance department interacted appropriately with the FDA, don't you think that it would be important to know what their standard operating procedures are?
MR. SCHMIDT: Object to form.
THE WITNESS: In some circumstances. But I think here I think that the documents of the analyses that they did, by my review, were adequate.
BY MR. JONES:
Q. Other than the FAERS database from FDA, what other safety databases are available from government regulators worldwide?
A. Well, there is a -- there's a European database. There's actually different names for it. But one of the databases is maintained in Sweden and it has a

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collection of adverse experiences from different regulatory bodies. The FDA reports make up about 60 percent of the reports in the database but the other 40 percent come from other countries.
Q. And what's the name of that database?
A. It's part of the EudraVigilance system. WHO is responsible for it. I can't think of the exact name at the moment, but it's the system that's based in Sweden.
Q. Is it the one from the Uppsala Monitoring Centre?
A. Yes, it's in Uppsala, Sweden.
Q. Okay. Did you say EudraVigilance?
A. Well, EudraVigilance is one of the descriptions of the European pharmacovigilance databases.
Q. Do you know, does Eudra, is EudraVigilance and WHO the same data source or does EudraVigilance feed into WHO? Do you know?
A. My understanding is EudraVigilance feeds into WHO, but I'd have to review to see the exact relationships. But there is -- the Swedish database is the other large database.
Q. So is the Swedish database something different from WHO?
A. No. That's the WHO-sponsored --
Q. Okay.

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A. -- database that has U.S. and other country data in it.
Q. Do you know what other countries report to WHO?
A. My understanding is that it -- it's -- the next largest collection come from the European Union. I don't -- I'm not sure what the reporting rate is for different countries.
Q. Can you turn to Page 12 of your report.
A. Okay.
Q. Okay. This is -- this isn't very helpful for me to read it sideways.
A. I have it in front of me if -- but --
Q. This is the -- this is from Page 12 of your report, the "Hierarchy of Study Design and Evidence For Drug-Associated Adverse Effects."
Did I read that correctly?
A. Yes.
Q. Now, did you make this chart or did you pull this from somewhere?
A. No. I made this chart.
Q. Okay. And "Hierarchy of Designs (Strongest to Weakest)," and then you have, "Adverse Effects assessed prospectively before adverse event?" "Controls for selection Bias/and Ascertainment Bias?" "Can estimate relative risk or hazard compared to control group?"

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And, "Can study rare events?"
Did I read that correctly?
A. Yes.
Q. Okay. And so it -- as it relates to pseudotumor cerebri, we've established that's a rare event; right?
A. Yes.
Q. Okay. So a randomized, controlled trial is not going to work to study that rare event; correct?
A. That's correct. They just can't be big enough.
Q. Okay. And registries or uncontrolled cohort studies, that's not going to work either; right?
A. That's correct.
Q. Okay. And then you say maybe for controlled cohort studies, enroll patients starting a new drug and compare it to similar patients not taking the drug. You say maybe.
Why maybe on that?
A. Well, for registries and other uncontrolled cohorts, the biggest -- well, there's two issues, but one of the more important ones is that even for two drugs in the same class, the types of patients that are prescribed one drug versus another may be very different.
So, for example, you know, relevant to Mirena, if there's a condition that's associated with obesity

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and there's recommendations to use IUDs in obese women, then even if you put together a cohort of, say, oral contraceptive users and Mirena users, you would have -- you wouldn't have controlled the selection bias. The patients would have been selected for a risk factor for a condition.
So there are ways that you can, with registries that you can try and match participants with one exposure to another but it's not done very often. Those are called case cohort studies.
So, generally speaking, you can't really control why the patient got the drug.
Q. I think you've been talking about registries and other controlled cohort studies; right?
A. Oh, okay. Where were you?
Q. Yeah. See, look up -- I'm up here on the screen.
A. Oh, okay.
Q. You had "no" there so you can't --
A. Yeah.
Q. I was up above that, the controlled cohort studies. You said maybe --
A. Oh, yeah.
Q. -- on can study rare events.
Why maybe?

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A. It may be that you have a circumstance of a very high-risk patient population that you could enroll in the cohort that has a high -- where the rate becomes common enough that you could study it.
Q. Okay. Would a -- how many individuals would it take in a controlled cohort study to study a rare event?
A. It depends how enriched the population would be by your -- by the types of patients that you enrolled.
So if the condition was -- you know, let's say that the clinical trial was 20 times too small but you could enrich the population in a cohort study to have the condition occur 20 times more often, then you may well be able to actually study it in that kind of a setting.
Q. And when you say enrich it, you mean enroll people that would be more at risk for the adverse event that you were studying.
A. Yes. For example, when they're studying heart disease, if you enroll smokers with high blood pressure and high cholesterol, you'll find more -- you'll see more heart attacks than you would if you just enrolled all comers taking the drug from the general population.
Q. Okay. I know from reading your report that you believe that obesity -- overweight and obesity and recent weight gain are risk factors for developing PTC;

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right?
A. Yes.
Q. Okay. So let's use that example and focus on the second category here.
A. Yes.
Q. You agree that not everyone who is overweight or obese develops PTC; correct?
A. That's right. It's still relatively rare. It's 20 times more common than non-obese but 20 times rare is still rare.
Q. Yeah. We'll talk about those numbers in a bit but --
So from a percentage-wise, how many -- what percent of overweight or obese women ultimately end up developing PTC?
A. Oh, from a percentage it's still well, well under -- I mean, if the rate is one in a hundred thousand for non-obese, approximately, or two in a hundred thousand, it's -- you know, we can discuss what the correct number would be but, you know, it could be as high as 20 per hundred thousand, but that's still pretty rare when you talk about how many patients you'd have to enroll to find PTC in cases.
Q. Right. So for purposes of studying PTC and obesity, the controlled cohort study that you say maybe

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can be used to study an adverse event or a rare adverse event, it's not really practical.
A. It doesn't work here, no. That's right.
Q. Okay.
A. That's right.
Q. And so then the --
MR. JONES: How much time do we have left?
VIDEO OPERATOR: Two minutes.
MR. JONES: I don't think we can get through the next one in two minutes.
THE WITNESS: All right.
MR. JONES: He only has two minutes on the tape.
THE WITNESS: Sure.
MR. JONES: So let's take a break.
THE WITNESS: Okay.
VIDEO OPERATOR: We are going off the record. This is the end of Media Number 2, and the time is 2:24 p.m.
(Recess, 2:24-2:41 p.m.)
VIDEO OPERATOR: This is the beginning of Media Number 3.
We are back on the record at 2:41 p.m.
BY MR. JONES:
Q. Dr. Feigal, we're back from break with a new videotape.

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Let's go back up to the controlled cohort studies that we were talking about, the second box.
A. Sure.
Q. That would be a prospective study; correct?
A. Right. And a cohort usually implies an exposure cohort, so you'd prospectively follow Mirena patients to see if they developed IIH.
Q. And you couldn't ethically put individuals in a prospective controlled cohort study without advising them that you were studying the risk of pseudotumor cerebri and whether or not they would develop it; correct?
A. Generally speaking, that would be correct. You generally disclose the purpose, the research purposes, of the study to the study participants.
Q. I mean, by and large, when you're looking at studying a potential association between levonorgestrel and PTC, you don't have a choice but to do a retrospective study, ethically; correct?
A. I think you could do them prospectively but the condition is so rare that I would agree with you that the only studies that are feasible are retrospective studies.
Q. Okay. Then going down to the next box, we have, "Case-Control Studies (enroll patients who have already

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had an adverse effect and compare similar patients without the adverse effect and look back to see drug use)."
A. Yes.
Q. Is that correct?
A. Yes, that's correct.
Q. Okay. And you have that that -- you can use that kind of case-control study to study a rare event; correct?
A. Yes.
Q. And that kind of study can estimate the relative risk or hazard compared to the control group; right?
A. Right.
Q. And you have maybe controls for selection bias and maybe controls for ascertainment bias; right?
A. Yes.
Q. Okay. So explain that to me.
A. Well, people who have a -- you know, here you're studying people who have a condition like PTC and people who don't, and when you're trying to evaluate the two groups of patients, just by virtue of the fact that the person has the condition, they may have had different medical care, they may have had more interactions, they may be -- have been exposed to more drugs because of their underlying condition.

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If you were looking at PTC in general, not just with -- as a risk for Mirena, you would probably be studying men and women and yet if the question was about Mirena, you would really only be interested in the women.
So you have to make sure that the selection of cases is representative and the selection of controls is as comparable as though you had set up a cohort study years ago and were following them forward.
And there are examples from the literature where they looked at dietary risk factors, for example, for pancreatic cancer but the controls came from the GI practice and the GI practice took care of many patients who were put on special diets.
Q. Uh-huh.
A. So then the pancreatic cancer patients generally had not been put on special diets and so they tended to show that -- in that particular study they raised the question of whether caffeine caused pancreatic cancer. But it was selection bias because the controls were a group that had been advised not to drink coffee because they had ulcers, for example.
Q. Okay. So --
A. So that's just an example of -- you just have to pay a lot of attention to the details to make sure that

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your cases and controls are representative of their, you know, respective populations.
Q. So selection bias is, you want to figure -- you want to try to do your best to find cases and controls that are pretty daggone similar?
A. Well, you want them to be each representative of their own population. So you've got the cases -- you've got the population that has the disease. You want your cases to be typical of those patients.
And then the controls are supposed to be comparable. Maybe they're supposed to be the same age, same age and sex. You know, you might control for that, but in other respects you want them -- you don't want them to be different in some way because, you know, in my example of trying to study diet in a population who had been put on special diets, they don't represent the general population's eating.
Q. Uh-huh.
A. So that's why you -- that's why selection matters.
Q. So on selection bias, what's the process for trying to minimize selection bias? What are good methods for developing a study that's going to minimize selection bias?
MR. SCHMIDT: Objection. Vague.

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THE WITNESS: Well, you'd start with your cases and you'd say, what are the cases that I want to study and is there a way that I can select a representative sample?
So if, for example, you've got -- you're at a university and the only -- you only see the most severe and unusual cases and all the milder ones are out in the general practices, you'd want a way to find, to select your cases from that whole, not just the university but from the general practice. In other words, you'd only be looking at part of the spectrum of the disease.
With respect to the controls, you want to make sure that the controls are the appropriate control group. You want them to be the same kinds of patients as the cases, except that they didn't develop the disease, PTC in this case.
And so if PTC can, you know, develop in a healthy person, for example, then you want to make sure that your controls could -- you know, largely reflected a healthy population.
That's often a challenge for hospital-based studies and medical records systems because the more interactions you have with a health-care system, the more times you're hospitalized or things, more likely you're not an average, healthy person --

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MR. JONES: Uh-huh.
THE WITNESS: -- that you're part of that spectrum that is more complicated.
BY MR. JONES:
Q. So that's the challenge to case controls is to -- one of the papers that was written years ago about this is the problem of spectrum and bias, being the right spectrum of patients and not being biased in the way that they're ascertained.
You may have more data on one group than the other and that makes -- that may make something artificially appear to be the case but it's just that you collected more information on one group. So that's a challenge.
BY MR. JONES:
Q. Say I was doing a study and you and Mr. Schmidt were my control group. Would it be acceptable for me to just walk out in the lobby of the law firm and select two other people and say this is going to be my control group?
A. No. You'd want a --
MR. SCHMIDT: Objection to -- object to foundation.
THE WITNESS: You'd want a little more care than that.

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If you look at how case-controlled studies do, they usually have a large population of controls. Controls are easier to come by than cases. So they usually take the cases that -- all the cases that they can find, because they're studying rare things so cases are precious, so they find all the cases. You have to make sure it's the right place that gets the right cases, as I mentioned before.
For controls, then they typically randomly select them from medical records, other kinds of ways to show that they're representative of the same population that the cases came from. So that's the selection bias aspect.
Then the ascertainment issue is you have to have the same access to information for the cases and controls. And so if, for example, you can contact cases because they're patients in your clinic but the controls, you know, you don't have a relationship with, you don't have a way to contact them, then you may have incomplete information on one group compared to much more complete on the other and that could create some biases.
So the attention is really on the details in the specific studies to do these right.

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BY MR. JONES:
Q. So on the selection bias, again, if you and Mr. Schmidt were my cases --
A. Yeah.
Q. -- would it be appropriate for me to get my controls by saying, you know, each of you call two of your friends and ask them if they'll participate in my study?
MR. SCHMIDT: Object to foundation.
THE WITNESS: Well, I chuckled because --
MR. SCHMIDT: Incomplete hypothetical.
THE WITNESS: -- because friend controls actually are one of the ways that people select controls in case-controlled studies. They actually ask people to identify someone like them in their community that they can approach and ask if they'd participate in a study.
More often, they come from what I would guess, say, convenience collections of people, such as you mentioned the lobby, but from the hospital, it would probably be other people in the clinic who don't have the condition. That's -- you know, that's commonly done. Or if you're selecting from a large health database and identifying them, then other participants in the health database.

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BY MR. JONES:
Q. And on this -- what did you call it? Friend control?
A. Yes.
Q. You said that people were asked to find a friend that's like them?
A. Yes.
Q. Doesn't that introduce some bias into -- you know, is Paul or is Mr. Schmidt like me or you like -- I mean, that introduces some biases as well.
A. No. That's absolutely right. No. No. So that's not a great way to do it. But that has -- that is a method that has been used.
Q. Okay. And then -- okay. So is there -- in terms of the controls for selection bias and ascertainment bias, can you ever eliminate in one of these case-control studies, absolutely eliminate selection bias and ascertainment bias?
A. No. And what the appropriate thing to do is to estimate what -- you know, what the -- how large a problem it could be.
So you shouldn't just discard studies because you can think of a reason that they might not be -- that there could be a problem with the study. You should also -- the responsible thing to do is to then assess

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how big of a problem could that be with this.
And you'll actually see that done in some articles, where they try and estimate what effects could be of things that, you know, could be biased in the study.
Q. And is there a way of -- is there an accepted way of quantifying the amount of selection bias or ascertainment bias?
A. The usual -- well, yes, but there isn't -- it isn't quite as standardized as calculating a P-value from a two-by-two table, which is really pretty, pretty well worked out. There's a lot more judgment involved. But there are techniques that involve modeling, where you make some assumptions about how big a bias effect could be and see how much that would change your result. That's one -- you know, that's one common method.
Q. And do you agree that -- well, strike that. Okay.
Let's move to the next box here, "Pharmacoepidemiology Studies (cohort or case-control designs conducted with insurance databases)." And you have yes, can study rare events; yes, can estimate relative risk or hazard compared to control group; again, we're at maybe/maybe on selection bias and ascertainment bias; and adverse effects assessed

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prospectively before the adverse event or adverse effect, you have yes/no on that.
Tell me why that's yes/no.
A. Well, ideally, when you're studying an exposure risk, you want to know that the exposure -- know about the exposure before you know about the adverse effect because we know that people who have had, you know, particularly a serious adverse effect spend a lot of time thinking about what did I do to deserve this cancer or this birth defect or this problem and they can remember a lot more drugs that they took and they can remember a lot more other behavioral kinds of things than someone where, you know, nothing is going on in their life.
And so you can't always -- in these databases, some of them are just cross-sections of one point in time and you don't have any historical record that the exposure occurred well before the event. And with the databases, it's less of a problem of memory because you are collecting but it's an issue sometimes that you just can't reconstruct the time sequence when two things, you know, two things appear together.
You can't tell from some databases, for example, when someone is diagnosed whether it's a new diagnosis, and if you don't know when the diagnosis started, then

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you don't know if they took the drug before the diagnosis. So that's a bit of a problem. If someone already has the condition when they take the drug, the drug couldn't have caused it. So that's the issue there.

Q. I'm just having trouble understanding how you can use an insurance database to study something prospectively.

A. Well, it's a retrospective/prospective.

Q. Okay. Explain that to me.

A. Well, if you had an insurance record that had five years' worth of data, for example, you can go back to that first year and find the people who do not yet have --

MR. SCHMIDT: Bless you.

THE WITNESS: -- the condition that you're looking at and you looked at the drugs they're taking and then you look at the second year and the third year and you can see all the things that are going on for that patient and then they develop the complication, and then you can see -- and then you can say, all right, they were exposed to these things before the event of interest and are people who have the event more likely to have had those exposures than the controls?

Now, a lot of studies can't establish the start

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of a condition. There are some conditions where the condition starts and then it may occur again later and you don't know that it's the first episode.

And then the other challenge if it's billing data is that you really have to validate that just because it's coded that way, they really had the disease, not that they're being evaluated, did they have the disease? Because they get coded the same sometimes.

But it's -- the different insurance databases have different quality of longitudinal information. And so if you have a disease that can appear and then, say, be quiet for five years and then appear again and you've only got two years of data, year before, year after, and they develop the disease in the second year, you don't know that they've had it before from an insurance database, you've just got the codes.

Now, the way you can get around that is in the systems where you also have access to the medical records. So some of the systems, like Kaiser, for example, with their databases, they start their task by looking at the codes but then they pull the charts and see what's really going on. So they use the codes to pull the charts and then they can do -- then they can simulate what a prospective cohort study is because they can identify an exposure and they can follow those

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patients forward -- you know, forward in time.

So those are sometimes called retrospective/prospective studies.

BY MR. JONES:

Q. Follow them forward in time based upon the treatment that they've had.

A. Yeah. You're looking at the exposures, whether you're looking at the risk from cigarettes, from obesity, or from a drug, but the point is you've got longitudinal information that you can rely on. And not all insurance databases do. So that's why it's yes/no.

Q. Okay. And then the next in your hierarchy is, "Case Series (a collection of patients with an adverse event)," and you have yes, it can study a rare event; no, it cannot estimate relative risk or hazard; then you get into the ascertainment and selection bias, maybe/no, and no.

A. Yeah. And our problem here is we don't have a control group. So we may have -- I may say I've got five cases in my clinic, but you'd say, compared to what?

Q. Uh-huh.

A. And then the question is, why do you have five cases in your clinic or your referral center or so forth?

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But the problem with the case series is that it doesn't have a control group so you really can't make a comparison. The case series are helpful in describing how patients do with a condition, what the spectrum is, what they look like, how many of them might have a factor, in this case, for example, obesity, but you don't have any control group to try and get, link it back to in terms of, you know, population.

Q. And when we talk about case series, this is what we see in medical journals, doctors writing in saying, hey, I've had this experience, I had five patients --

A. Right.

Q. -- in my clinic --

A. Right.

Q. -- and here are the details; right?

A. Right. Right. Right. The minimum number seems to be three to write them up but --

Q. Okay.

A. -- but before the journal editors will publish it but -- unless it's very unusual.

But yeah. So these are sort of the uncontrolled collections. They're a step up from an individual case report in that somebody has systematically tried to describe the condition they're describing. They're writing a paper about the condition, if you will,

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because these often come from the literature, or a company could do one as part of its evaluation. But -- and so it will have some uniformity in the way that it describes and assesses them but it won't have a control group. So that's why it's limited.

Q. Okay. You mentioned the individual case reports. So what you're --

A. Yes.

Q. -- talking about there is not Spontaneous Adverse Event Reports, you're talking about a health-care professional who writes something up?

A. No. It can be any -- it can be from any source.

Q. Okay.

A. It can be from any source.

The case series are almost always going to be written up by a health professional or a safety professional but the case reports, as we've talked about earlier, they can come from any source. You can learn about them from any source.

Q. And the individual case reports, the spontaneous reports, the quality of the data, I believe you would agree, is hit or miss.

A. Yeah, it's varied.

Q. Sometimes they're well documented?

A. Right.

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Q. Many times they're not; right?

A. Right. And then they're contradictory and there's, you know, the individual -- they vary in their quality.

Q. And with the case series, you get more detail because a health-care professional is kind of putting their reputation on the line by publishing something?

A. Well, and they're trying to write up --

MR. SCHMIDT: Object to characterization.

THE WITNESS: I think what -- whether it's their reputation or not, they're trying to write up and describe a specific thing. They think there's some commonality to those cases. So there's more detail and there's more -- they're more likely to note whether there's common features to the cases that might be a risk factor, although you don't have a control group.

With the individual cases, you don't have a control, you don't have any -- you know, you don't have anything to anchor those things to.

MR. JONES: Okay.

BY MR. JONES:

Q. And the Rai abstract, would that be -- on the first page, would that be what you would consider a case-control study?

A. It -- I think that's what he was trying or she

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was --

Q. She.

A. -- trying -- I'm sorry. She was trying to do. My -- but being an abstract, there's really not -- there's not very many details in the methods about where the controls came from.

And so, for example, you know, in terms of ascertainment bias, it wasn't clear if they had the ability to actually telephone the controls as well as the cases. So there was just -- because it's an abstract, it's -- you know, abstracts are typically 10 or 11 sentences long and often works in progress.

But that study is, I think, designed as a case-controlled study but there's a lot of questions about that study that we probably want to talk about.

Q. And it's longer than 10 or 11 sentences long; right?

A. I'd have to count them. But when I used to advise students writing abstracts, I'd say, you've got ten sentences, three for introductions, three for results, and three for conclusions.

Q. Well, we'll look at it in a little bit.

A. All right.

Q. And you've mentioned, you know, that there's some information, based upon your review of that

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abstract, that you don't know whether, for instance, they had the opportunity to telephone controls; right?

A. Well, that's right. We don't -- there are some things that we don't know and -- although we'll get to this, the other thing that was unusual was the number of cases that he identified. When you look at some of the other -- or she identified.

When we look at some of the other literature, you'll see far fewer cases being identified by a combined effort of nine or ten university hospitals. So if a paper ever is written about that, we'll be able to answer some of those questions.

But it's -- the other possibility, which gets to selection, is it could be that the net was cast very broadly in terms of trying to obtain possible cases. And we know that the ICD-9 codes, when they're used for PCT, are actually only referring to an actual case of PTC about half the time. So we just don't know that about that abstract.

Q. Right. And you're speculating that in that particular study that only 50 percent of the cases identified by ICD-9 code might not be PTC cases; correct?

A. Well, that's right. There's no description. Normally, in a study, in a study that has ability to

write a longer methods section, they would describe how they validated their selection criteria and how they know that the cases are PTC.

Q. Are you aware of whether or not those authors have a full article in process?

A. I don't know one way or the other.

Q. In progress?

Have you heard from anyone, any of your colleagues in the medical community, that these authors have developed a full article that's now under -- being subjected to the peer-review process?

A. No, I don't know one way or the other.

MR. SCHMIDT: It's kind of like the next J. K. Rawling's book. All we hear is chattering. Might be coming, it might not be.

MR. JONES: Do share.

BY MR. JONES:

Q. An individual --

MR. JONES: That's a good joke.

BY MR. JONES:

Q. An individual spontaneous --

MR. SCHMIDT: That will be my contribution. I'll shut up now.

BY MR. JONES:

Q. An individual spontaneous case report is the

observation of an adverse event associated with a drug; correct?

A. That's correct.

Q. And these reports may be useful in some cases to detect signals of a potential association between outcomes and medical treatments; correct?

A. That's correct.

Q. And the FDA and product manufacturers use spontaneous reports to detect new potential safety issues; correct?

A. Yes.

Q. And these reports, even when aggregated, cannot provide estimates of incident -- incidence rates or prevalence for the product, let alone provide comparative rates between products; correct?

A. Yes, that's correct. And FDA has said that as well.

Q. So you can't use spontaneous reports to try to determine what the incidence rate is; correct?

A. That's correct.

Q. And if someone tried to use spontaneous reports to estimate incidence rates, that would be contrary to what FDA says; correct?

A. Well, not --

MR. SCHMIDT: Object to characterization.

THE WITNESS: Not exactly.

I think that you can make some estimates, with limitations, if you know the total sales of the product but the problem with spontaneous reports is that there's always a degree of underreporting.

So if you were to get a number of reports that when you divided it by your known sales of the product, for example, and that was already more reports than you would expect from the background rate and even though you couldn't estimate the incidence, you'd say this looks like we've got an association with the drug.

On the other hand, if it's a serious condition where the reporting is generally better and the rates are below or similar to the background rates, that's reassuring but it isn't a reason to stop looking.

You -- but that is something that companies commonly do is they compare the rates compared to sales, and that helps also understand over time if the reporting is going up and the sales are going up proportionally, then you may be looking at something that isn't changing.

On the other hand, if the reporting is going up and the sales are flat, then it may be a problem that increases with time, with, you know, more prolonged exposure to the same number of patients.

So there are some clues, but you just can't do epidemiology from aggregated case reports.

BY MR. JONES:

Q. Can you point me to anything and -- any FDA guidances, FDA regulations, statutes governing FDA that says if you have sales data, then you can use spontaneous reports to provide estimates of incidence rates or prevalence for the product?

A. Not in those exact terms but, you know, if you look at the quote that starts on Page 13 and goes on to Page 14, FDA is talking about the factors by which you evaluate the number of reports you have.

So, for example, they point out publicity is something that can increase the number of reports, or how long the product has been -- has been -- the product has been marketed.

So I think these are more qualitative things that you evaluate. So you do look at your sales and you do, you know, calculate some numbers but you use the information more qualitatively. You can't assert that that's the known incidence or prevalence of the adverse effect in all users of the drug because you just don't have all the reports.

Q. I'm trying to find in the quote that you've cited me to anywhere where it discusses sales data, if

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you have sales data, that you can use spontaneous reports to provide estimates of incidence rates or prevalence for the product.
A. Well --
Q. Can you point me to that?
A. -- it's not in the report, but it isn't what I've said.
What I've said is that you take that information into account. You know, they point out other factors, such as publicity or length of time on the market, which may relate to cumulative exposure and sales. These are factors to consider when you look at why are you getting reports and how many you're getting but FDA's bottom line is that you can't calculate accurate incidence or prevalence rates.
Q. And when you talk about FDA talking about publicity and time on the market, extent of use, it's not talking about calculating an incidence rate from that data, is it?
A. No, it's not. It's talking about -- although you can do that. But it's talking about evaluating the relationship of the reports, the reports to the total sales.
And it's a common practice in industry to sort of say, if these were all the reports we had and this is

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the incidence and this -- if this is all the reports and this is the sales, what would the incidence be, you'll see that done. But they don't -- I think everyone will acknowledge that doesn't calculate accurate incidence and prevalence.
Q. Going back to your hierarchy of study design and evidence for drug-associated adverse effects, are you aware of any efforts by Bayer to -- strike that.
Are you aware of any case-control studies that Bayer has conducted to study the potential association between pseudotumor cerebri and Mirena?
A. No, I'm not. And I think even the Rai article, you know, illustrates how difficult it is to actually organize those studies.
Q. And are you aware of any efforts by Bayer to conduct a pharmacoepidemiology study to examine the potential association between pseudotumor cerebri and Mirena?
A. No, I'm not aware of any pharmacoepidemiology studies that have been completed and I don't recall reviewing documents about plans so -- but there certainly -- there certainly -- I'm not aware of any that have been conducted.
Q. Have you been a part of designing pharmacoepidemiology studies in your career?

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A. Yes, I have.
Q. Okay. And so you've looked at the Rai study --
A. Yes.
Q. -- from the abstract.
A. Yes.
Q. How much would you estimate a study like the Rai study would cost?
MR. SCHMIDT: Objection. Foundation.
THE WITNESS: If it involves contacting patients, chart reviews, certain amount of work before, the individual patient cost, once identified, is probably in the range of three to four thousand dollars per patient. The upfront work of doing the database work and all of that type of stuff, maybe a few, you know, a few tens of thousands of dollars.
So I can't do the math in my head, how that works out, but those are sort of typical costs for studies like that today.
BY MR. JONES:
Q. So are you of the understanding that the patients who participated in the telephone interviews in the Rai study were paid three or four thousand dollars apiece?
A. No. That's the labor cost of the study personnel from the time they identify a patient, do the

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interview, fill out the case report forms, get the data in the database. If you just add up the hours of their time, that would be my estimate. Could be a little less than that. But, no, that's assuming you're not paying the patients, that the patients are just voluntarily participating.
Q. And I think that maybe that study said that they were volunteers.
A. Yes. That wouldn't surprise me.
Q. Do you agree that generally rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event?
A. I don't think they're --
MR. SCHMIDT: Objection.
THE WITNESS: I don't think they're usually employed. They're a tool that's being used more and more as the databases become more accessible.
It's only been within the last half decade that the databases linked pharmacy records with medical diagnoses. So there was a lot of pharmacoepi in the past that was simply based on studying patterns of drug use to try and guess what was going on medically.
MR. JONES: I --

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THE WITNESS: So that the tools have gotten better and better and better. So I wouldn't say usual, but it's a tool that's being employed more often, more and more often today.
BY MR. JONES:
Q. Will you turn to Page 13 of your report.
A. Yes.
Q. And do you see down at the last full paragraph where it says, "According to FDA"?
A. Yes.
Q. Can you read that into the record.
A. Yeah.
Rigorous pharmacoepidemiology --
Q. Can you start with the beginning of the sentence.
A. Okay. According to FDA, rigorous pharmacoepidemiologic studies, such as case-controlled studies and cohort studies with appropriate follow-up, are usually employed to further examine potential association between a product and an adverse event.
Q. Okay. So you did say "usually employed" in your report; right?
A. Well, the FDA said that. And they're actually not referring to the kind of insurance database studies that I was jumping to the conclusion that we were

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talking about. They're talking about the typical -- the traditional types of case control and cohort studies where they actually enroll patients in those studies rather than just study their records.
Q. If you don't understand a question, feel free to ask me to clarify it.
A. Yes.
Q. Okay?
A. I apologize if I misunderstood.
Q. Isn't it true that FDA does not require that a causal relationship between a product and an event be proven before allowing it to be added to the product labeling?
A. Yes, that's correct. The standard is reasonable evidence of a causal association.
Q. That's the standard for what?
A. That's the standard for a warning or precaution. The standard for an adverse reaction is some basis to believe there's a causal association.
Q. Some basis to believe.
A. Yes. That's been the standard since 2006.
Q. And what's the standard for adding an event to a product label in the post-marketing experience section?
A. Well, that is the standard: Some basis to believe that there's a causal association.

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Q. Is it your testimony and belief that every warning and adverse reaction listed in the current Mirena label is supported by reasonable evidence of a causal association?
A. I haven't --
MR. SCHMIDT: Objection. Foundation.
THE WITNESS: I haven't really looked. You know, I've only really -- in my work with Mirena have really only looked at perforation and IIH so I don't really have any opinions about the others.
BY MR. JONES:
Q. But you're giving an opinion in this case that the labeling was adequate; correct?
A. Yes; with respect to PTC.
Q. When is the last time you reviewed the label?
A. I think I've looked at the label within the last week.
Q. And based upon your -- does FDA allow anything in a product label in the warnings or adverse reactions section that is not supported by reasonable evidence of a causal association?
A. Generally speaking, no. That is the standard for a warning and precaution.
Q. And you said the some-basis standard related to the adverse reactions portions of the label; right?

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A. Yes.
Q. And then I asked you about what the standard is for the post-marketing experience section of the label and you suggested that the standard is the same; is that correct?
A. Yes. The adverse reactions section has two sections, one of them is adverse reactions from clinical trials. And when they're controlled clinical trials, the basis to believe that there's a possible causal association is the fact that they're -- that the rates are different in one group than the other, although sometimes they'll actually also include information showing comparisons of things where there's no difference.
But, generally, where there is a difference, it's because there's more of the adverse event in the drug than in, for example, the placebo arm.
The post-marketing experience section often begins with, has been reported, and they list the things that have been reported where there's some basis to believe there's a causal association.
Q. Has --
A. So the standard is the same but the source of the evidence is a little different. One comes from a clinical trial and the other comes from mostly

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spontaneous reports and some, the literature.
Q. Has pseudotumor cerebri been reported in relation to Mirena?
A. Yes, it has.
Q. Is there some basis to believe that there's a causal association?
A. In my opinion, no.
Q. And you don't think that the Rai abstract provides some basis of evidence of a causal association?
A. No, not as written, it does not.
Q. What's it going to take to satisfy you that there is some basis of -- for believing there's a causal association between Mirena and PTC?
MR. SCHMIDT: Objection. Foundation.
THE WITNESS: If there was a study which could demonstrate that the rate was higher than the background rate after controlling for weight and recent weight gain, then I think if there was an increased risk of -- that was unlikely to be due to chance, that would be some basis to believe that there was reasonable evidence of a causal association.
BY MR. JONES:
Q. What do you define as recent weight gain?
A. Well, some of the case-controlled studies that have looked at the role of obesity have shown that as a

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risk factor for recurrence, as little as 7 percent total body -- total body weight is correlated with a -- is correlated with recurrence.
And the authors also commented that weight loss of 7 percent also is about the average weight loss for patients where loss of weight was associated with resolution of the syndrome. So that's -- that would be one, you know, criteria to start. If you had enough information to document that kind of level of change, then that would fit with the current literature.
Q. Okay. You answered the weight gain part of it. What do you define as recent?
A. I don't know if I have a working definition. It would be recent in relationship to the development of the PTC.
Q. Can you point me to any scientific literature anywhere in the world that defines what recent is in relation to recent weight gain and its risk factor --
A. I don't --
Q. -- for the development of PTC?
A. I don't recall how it was defined in the studies where you used that term.
I would go back and look to what were the definitions the authors used where they found it was a risk factor and that would probably be a reasonable

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definition to use. But I don't -- sitting here today, I don't know what that is.
Q. Do you agree that not all patients who have PTC experience a resolution of symptoms with weight loss?
A. I think that would probably be correct, yes.
Q. FDA does not receive reports for every adverse event or medication error that occur with a product; correct?
A. That's correct.
Q. And many factors can influence whether or not an event will be reported, such as the time the product has been marketed and the publicity about an event; correct?
A. Yes, that's correct.
Q. And are you aware of any publicity about the connection between the potential association between Mirena and pseudotumor cerebri?
A. I personally have not come across any publicity about this. May be out there but I have not noticed any.
Q. So you can't testify or you're not giving an opinion that publicity about the product or pseudotumor cerebri contributed to an increase in reporting of events involving Mirena and pseudotumor cerebri?
A. No, for this specific case, I don't know of any publicity associated with the potential risk.

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Q. You agree that reporting of adverse events by physicians and patients is both voluntary and spontaneous; correct?
A. Yes.
Q. What's a disproportionality analysis?
A. It is a -- that's a term that's usually used to describe an increased proportion of reports of a side effect for one drug compared to other drugs reporting that same side effect.
So if one drug, say, 2 percent of its side effects were PTC and another drug was 1 -- and all other drugs was 1 percent of the reports with PTC, that would give you a reporting ratio of 2, you know, 2 percent compared to 1 percent, and that -- one of the descriptions of that is a disproportionality analysis.
Q. And I understand from your report that you don't believe that a disproportionality analysis can establish a causal association between an event and a drug; correct?
A. Yes, that's correct.
Q. Okay. And wouldn't the converse be true as well? A disproportionality analysis can't rule out a causal relationship either, can it?
A. I would agree with that. Yes, I would agree with it.

The analyses are used primarily to detect signals, and so it could be used to say there's no signal, but that's only indirect evidence about whether there's a potential relationship or not.

Q. Other than checking the work of plaintiffs' experts in this case, did you conduct your own independent disproportionality analysis?

A. For this case, for this -- and for this condition, I -- what motivated me to do it was reading the reports by the plaintiffs' experts, and that's when I went to the database and repeated their analyses.

Q. Okay. But you just repeated their analysis, you didn't try to conduct your own analysis; correct?

A. Well, I ran variations on their analyses, not all of which I think they reported.

So, for example, I also looked to see what happened when you used the -- when you restricted the cases to women of childbearing potential, for example.

So I did something -- I did analyses that they didn't do but I looked to see where their numbers came from and then I did variations on their analyses.

Q. Did you put those in your report ?

A. Not all of them, no, I did not.

Q. What database did you use?

A. I used OpenVigil, both 2.0, which Dr. Ross

initially used, and 2.1, which Dr. Etminan used.

Q. When you're talking about case-controlled studies, there is a way to control for confounders, isn't there?

MR. SCHMIDT: Objection. Vague.

THE WITNESS: There are methods to control for confounding, yes.

MR. JONES: Okay.

BY MR. JONES:

Q. And one would be a --

MR. SCHMIDT: Bless you.

BY MR. JONES:

Q. -- sensitivity analysis?

A. No. I think that's more an analysis of the hypothetical effects of confounders.

Usually if you say you've controlled for confounders, you've measured a confounding variable and you've adjusted for it in some way. You've either done at multivariate analysis that includes both the drug and a confounder so you'd, for example, simultaneously estimate the risk of Mirena and weight and weight gain or you control for confounding in the selection of your controls.

So if you selected a case and you found that that case had a BMI of, say, 35, and then you picked a

control whose weight was between, you know, 33 and 37, you would be able to control for weight as a confounder even though you didn't estimate the risk of weight by using that design.

So control usually means that you've got the variable in the patients that you're studying. Sensitivity analysis means you've done a bunch of hypothetical exercises to see what could have happened.

Q. But you're -- maybe control was the wrong word. You can account for confounding bias; correct?

A. Yeah, I'd say the controls account for it and the modeling assesses it, assesses the potential, the hypothetical role.

They're slightly different. I may be being too picky about the words. I think it's appropriate to after you've done an analysis where you were unable to measure confounders to try and model what the potential effects could be.

Q. Have you ever used a sensitivity analysis in any of the studies you've been involved in?

A. Yes.

Q. So it's an accepted scientific method; correct?

MR. SCHMIDT: Objection. Vague.

THE WITNESS: Well, there are various methods and they have their strengths and weaknesses. They're

the methods that are used to actually assess how robust your result is, could your result be due to something that you haven't measured or haven't accounted for.

BY MR. JONES:

Q. Do you know Sebastian Schneeweiss, S-C-H-N-E-E-W-E-I-S-S, at the Division of Pharmacoepidemiology and Pharmacoeconomics at the Brigham & Women's Hospital and Harvard Medical School?

A. I know of Dr. Schneeweiss. I think it's Schneeweiss.

Q. I'll take your word for it.

A. But I had trouble with the gender of Dr. Rai so I'm not sure how good I am on people today.

But I know of him, yes.

Q. Okay. And is Dr. Schneeweiss respected in the field of pharmacoepidemiology?

A. Yes, I believe he is.

Q. Okay. And are you aware of his "Sensitivity Analysis and External Adjustment For Unmeasured Confounders in Epidemiologic Database Studies of Therapeutics"?

A. Yes. As I recall, Dr. Etminan may have identified that paper as the source of the methods that he used, and when he did that, I went and looked at that paper. I didn't -- I'm looking to see if I referenced

that. And I may not have referenced it, but it should be in my total list, because I have that paper, I've seen that paper.

Q. And if I understand it, you didn't have any problems with Dr. Schneeweiss's sensitivity analysis, your problem was with the data that Dr. Etminan used to plug into the Schneeweiss spreadsheet; correct?

MR. SCHMIDT: Object to form.

THE WITNESS: Well, there are two issues.

I think Dr. Schneeweiss's method is a reasonable method to assess the effect of a potential confounder.

There were sort of two issues with Dr. Etminan's numbers. One is the numbers that he used. It depends on which tables we're talking about from his report or from his paper but, for example, when he was looking at disproportionality, he was looking at reports rather than cases, and it's more important to look at cases because reports -- there's almost two reports for every case, so you just have a number of duplicates.

So that's one issue with the cases. And you should also, you know, be comparing to women and so forth. So that's an issue with the tables.

But the other issue that I would have with Dr. Etminan is the range of values that he used to put in his modeling and in the way that he described the

results of his analysis.

So I had a number of issues with how Dr. Etminan applied Dr. Schneeweiss's methods but I don't have a problem with Dr. Schneeweiss's methods themselves.

BY MR. JONES:

Q. In going to Page 15 of your report, the last sentence of the paragraph under Item Number 7 reads, while a manufacturer only has access to its own data, FDA has access to data from all manufacturers relating to the drug, which can often provide important adverse event information.

Did I read that correctly?

A. Yes, you did.

Q. Okay. And isn't it true that Bayer has equal access to FDA data?

A. No. They have access to the AERS database that -- but in the example I gave where, you know, a company might use another company's product in clinical trials, clinical trials adverse events don't go into the AERS database.

Q. So when you're talking about data, you're talking about clinical study data.

A. Well, I mentioned -- that's one of the sources here, but yes. I mean, the -- when a drug becomes a standard -- and I'm not sure there -- how many of them,

how many contraceptives have compared themselves directly to, you know, to Mirena -- then it becomes used as a control in other studies that the company doesn't have access to.

So, for example, Mirena did a large post-marketing study with 60,000 women comparing Mirena users to copper IUD users so they had a lot of data about copper IUDs that were in study reports and things but they weren't in the AERS database and they weren't data that the copper IUD manufacturers had direct access to.

Q. Do you know whether or not Bayer has access to the Norplant study data?

A. I don't know. I don't know to what extent they have that data.

I know that they have a follow-on product to Norplant and that there's been -- but I'm not sure what the relationship is with the companies in terms of exchange of data and exchange of original records with respect to Norplant. It was originally brought to market by Wyeth?

Q. Is that what you think?

A. Well, let me look. Because I actually wrote down -- I wrote up a bit about Norplant so hate to --

MR. SCHMIDT: Objection to the memory test.

THE WITNESS: Hate to provide --

MR. JONES: I didn't ask him a question.

THE WITNESS: You didn't. You know, you didn't.

MR. SCHMIDT: You said, is that what you think?

THE WITNESS: Well --

MR. SCHMIDT: I never object in the ether.

MR. JONES: I didn't ask him a memory test.

MR. SCHMIDT: To be fair, this is about my fourth objection today.

THE WITNESS: Well, as I recall, Norplant was not the original, but at the time that some of the issues around Norplant came up Wyeth-Ayerst was the NDA holder.

MR. JONES: Okay.

BY MR. JONES:

Q. Have you ever heard of a company called Leiras Oy?

A. Yes.

Q. And you would agree that Leiras Oy is now Bayer Oy; correct?

A. My understanding is that, yes, that Bayer -- that that's now part of the Bayer family of companies.

Q. Okay. And did you know that Leiras Oy manufactured Norplant on behalf of Wyeth?

A. I think I did know that, yes.

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Q. And did you know that Leiras Oy marketed Norplant outside of the United States back in the '90s?
A. Yes, I did know that.
Q. Have you been provided in this case any adverse event data related to Norplant from Bayer's lawyers?
A. I do have some information about the adverse events and the literature, the medical literature, about Norplant's safety as it relates to these cases and those are cited in the report.
Q. Do you know what an Adverse Event Report is?
A. Yes.
Q. Have you been provided with any Adverse Event Reports related to Norplant and pseudotumor cerebri by Bayer's lawyers?
A. Not that I recall.
Q. Did you ask Bayer's lawyers for any of that information?
A. No, I did not. I reviewed the circumstances under which Norplant came to have a warning about pseudotumor cerebri.
Q. Did you know that Wyeth sent out a dear-health-care-professional letter in the 1990s advising health-care professionals about the potential or advising physicians about the change to the label adding pseudotumor cerebri?

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A. Yes, I'm aware of that.
Q. Have you ever seen that dear-health-care-professional letter?
A. I think I have, although I don't recall. But I think I have. I'm familiar with the labeling change.
Q. Have you seen the dear-health-care provider letter within the scope of your work on this case?
A. Well, that's when I would have seen it. I don't recall sitting here if I've seen the letter. I'm familiar with the labeling change.
Q. Okay. But you don't know whether you've seen the letter or not?
A. I think I have, but I don't know for certain.
Q. Did you ever ask Bayer's lawyers to provide you with that dear-health-care-provider letter?
A. No, I didn't ask to see the letter. But I don't know if they sent it to me and that's -- if that's in the material that I've reviewed.
Q. You don't know whether it's on your reviewed or relied upon list?
A. I could look, but I don't know specifically if it is or isn't.
Q. In Footnote 10 of your report on Page 15 you say, you quote from a source and say, the authors go on to comment, quote, even in the cases when the event

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appears in the product labeling, many factors other than a true causal relationship between a drug and an event may influence the labeling, such as some class effects, litigation and publicity.
Did I read that correctly?
A. Yes.
Q. And what source are you citing for that?
A. Apologize that that isn't clear, but that is a -- I believe that is a -- refers to the Levine article, which is Reference 36 in the end notes, and that's just a -- it's a quote from the Levine article.
Q. And do you believe FDA allows events to be listed in product labeling when there is something other than a true causal relationship between a drug and an event, such as litigation?
A. Well, that's an interesting question.
The event is usually listed first and the litigation comes later so -- so I can't think of a situation where litigation reports resulted in what was the first notice of an adverse event and was the result of a labeling change.
Q. So you believe that an event listed in a label usually leads to litigation?
A. No.
MR. SCHMIDT: Object to characterization.

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MR. JONES: I was trying to figure out --
THE WITNESS: No, I didn't say that. But where there are -- you know, FDA, for example, has written about the situation with Accutane where they point out in one year 97 percent of the reports were from litigation reports and they were commenting on how that made -- how that distorted disproportionality analyses when there was a large number of litigation reports. That was an FDA comment.
So they're -- but what I was saying was the opposite, which is I can't think of a situation where litigation itself was the first reasonable evidence of a causal association that led to a labeling change. Usually something leads to the labeling change. Some of those -- some things in labeling do lead to lawsuits but certainly not all.
BY MR. JONES:
Q. When you talk about litigation reporting, you're talking about the company is reporting to FDA that they're involved in litigation; isn't that correct?
A. That's right. Well, what they're reporting is -- actually, what they do is they report the facts of the case that are described in the legal document, which may be a Complaint, for example. As -- and then the source down at the bottom, the way FDA identifies those

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as a report from a lawyer is that many companies then identify that the reporter was a lawyer.
Q. Well, I'll tell you something that has bothered me throughout this case is that it doesn't indicate that it is the defense lawyer, the company's lawyer, who is reporting that.
Do you realize that?
MR. SCHMIDT: Object to the preamble.
THE WITNESS: Actually, I don't think that's the case. I think that the reporter in that case is actually the attorney who's filed the Complaint. But, I mean, that's my understanding of who the reporter is. The reporter is the person who sent in the information to Wyeth, not the people at Wyeth that evaluated the information, which in a legal case would involve an attorney.
BY MR. JONES:
Q. Well, I've made no reports to FDA but I see that it's listed as a lawyer report in Bayer's documents so --
A. Well, I think --
MR. SCHMIDT: Object to lawyer testimony.
THE WITNESS: -- the way that it would occur is that if you made a compliant about a case, one, if they can identify it as a case they already know about, if it

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has new information, then they could file a new report to the same ISR, the same study report, and say this is a supplement. If it's a patient that they didn't previously know about, then they would -- the company's practice would be to fill out the MedWatch form based on the information in the Complaint.
BY MR. JONES:
Q. You agree -- I'm sorry.
A. Yeah. And the reporter then would be the attorney who submitted the complaint because that's the source of the information about the patient.
Q. You agree that labeling is the key source to assure safe use of a drug product; correct?
A. I would agree with that. It's one of the most important sources about the safety information about a product, yes.
Q. And a label is intended to provide physicians with a clear and concise summary of the information necessary for the safe and effective use of the drug; correct?
A. Yes.
Q. An FDA-approved label is intended to assist a prescriber in making decisions for individual patients; correct?
A. Yes, that's correct.

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Q. And you agree, don't you, that contraception choice is also a decision to be made by the individual patient; correct?
A. Yes, I agree with that.
Q. You agree that labeling is the FDA's principal tool for educating health-care practitioners about the risks and benefits of approved products to help ensure safe and effective use; correct?
A. Yes; both directly as prescribing information and then all of the promotional materials that are based on the labeling that are derived from the labeling. The label plays an important role there.
Q. And FDA-approved labels are supposed to be balanced and accurate; correct?
A. That's the standard for promotional materials. But, yes, labels, generally speaking, are going to be balanced and accurate.
Q. And warnings describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if adverse reactions occur; correct?
A. Yes, that's correct.
MR. JONES: How long have we been going on this tape?
VIDEO OPERATOR: One hour, eight minutes.

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MR. JONES: Why don't we take a little break.
VIDEO OPERATOR: We are going off the record. The time is 3:49 p.m.
(Recess, 3:49-4:01 p.m.)
VIDEO OPERATOR: We are back on the record. The time is 4:01 p.m.
BY MR. JONES:
Q. Dr. Feigal, welcome back.
You note in your report that the Mirena prescribing information label also contains information for patients; is that correct?
A. Yes, there's a section that's called that. That section is actually written for doctors to give them guidance on what to tell patients about. So it's not written to be given to patients but it's written for doctors to give recommendations on what to include in providing information about the product.
Q. And nothing in there warns of the potential of developing pseudotumor cerebri with Mirena usage; correct?
A. That's correct.
Q. Okay. And do you understand that there was also a Patient Information Booklet that was also given to the patients at the time of insertion?
A. Yes.

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Q. Okay. And that also contains no reference to pseudotumor cerebri, does it?
A. That's correct. It does not.
Q. Do you agree that before 2007, FDA had no authority to order label changes?
A. No, not exactly. They -- after 2007, they had very specific authority to order label changes with certain time frames, but before that time, FDA had a number of ways that they would accomplish getting labeling changes that FDA felt were appropriate.
Q. Well, can you cite me to the specific authority that allowed FDA to order label changes before 2007?
A. Yes. The authority is based on the misbranding, that if FDA determines that a label is inadequate, doesn't meet the labeling standards, then the product must be revised to address the issue that FDA is concerned about in order for it not to be misbranded.
So FDA generally didn't have to resort to actually actions against products. Part of what FDA does with companies is communicate with them frequently about changes that it asks the companies to evaluate and incorporate in their labeling or make a proposal to them as to what to do instead or why it may not be needed.
Q. Before 2007, if a product was misbranded, FDA could force the removal of the product from the market;

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correct?
A. They could. They could do -- most common regulatory action would be a product seizure. But yes, they could.
Q. But there was no specific legal authority before 2007 for FDA to order a label change; correct?
A. Not in the same way that it was written after 2007. But before that time, if you go through the records, you'll find any number of times where FDA sends companies labeling that it wants, sometimes class labeling -- that almost always comes from FDA -- but also to address safety problems that have come to FDA's attention that the company may not even be aware of yet.
Q. Can you look at Page 18 of your report.
A. Yes.
Q. I want to point out that there's a difference in font between the body of the report and the footnotes.
Do you see that?
A. Yes.
Q. Okay. And why is that?
A. Probably just the vagaries of Microsoft Word that I don't -- when things -- particularly if I've cut and pasted from one document to another, sometimes the formatting from the other document gets carried over. I try to clean that up but --

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Q. Did someone insert these footnotes for you?
A. No. This is all my -- this is all my own work.
Q. You wrote this report?
A. I did.
Q. Do you agree that the importance of safe and reliable contraception is beyond question?
A. Yes, I would agree.
Q. Do you agree that several major categories of contraceptives are widely available?
A. Yes, I would agree with that.
Q. Do you agree that several reversible drugs and device contraceptive methods are available that are not hormonal?
A. Yes. They vary in their effectiveness, but yes, there are several -- there are many options that women can choose from.
Q. Are you aware of any Adverse Event Reports involving the copper IUD ParaGard and pseudotumor cerebri?
A. I do not -- I don't -- I'm not aware of any. No, I'm not.
Q. You mention in your report an ACOG bulletin that says that levonorgestrel IUDs may represent a particularly sound choice. Does that sound correct? For obese women. Sorry.

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A. Yes, they -- yes, I did cite an ACOG document where the product is recommended for obese women.
Q. Did you know that one of the ACOG bulletins that you cited to was prepared by a physician who is a Bayer consultant for Mirena?
MR. SCHMIDT: Object to the characterization.
THE WITNESS: No, I don't know -- I didn't look to see in the document the disclosures from the authors of the bulletin.
BY MR. JONES:
Q. Do you think that there should be disclosures in the ACOG bulletin if it was prepared by a Bayer consultant for Mirena?
A. Possibly. It depends on the circumstances of the relationship, the consulting relationship. Most journals have their own policies which they ask their authors to follow so...
Q. You mention in your report that LNG, levonorgestrel, is an active ingredient in 54 NDAs and ANDAs; is that correct?
A. Yes.
Q. And you say that the FDA labeling database lists 75 separate product labels where LNG is an active ingredient; is that correct?
A. Yes.

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Q. Did you do any searches of either the FDA database or the WHO database to determine how many Adverse Event Reports had been made alleging the development of pseudotumor cerebri in relation to use of these 75 separate product labels?
A. The databases aren't organized that way. The databases are organized by -- the databases are organized by the drug and by the drug product name.
So you can separate out Mirena in your searches by searching on the drug product name, Mirena. If you search on levonorgestrel, you could identify the levonorgestrel combination birth-control pills by also specifying the estrogen component.
I did do searches initially of levonorgestrel alone for all products but because I was largely looking at the searches and with respect to Dr. Ross's and Dr. Etminan's work, I mostly focused on the Mirena reports.
Q. How many of the 75 separate products were levonorgestrel combined with something else?
A. Probably a very large number of them.
Q. Most of them; right?
A. Probably. You can tell that by the number of generic birth-control pills that have been approved as ANDAs.
Q. And when you go into the WHO database and

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search, as you noted, you can put in levonorgestrel; right?
A. Yes.
Q. And the adverse event that you are interested in; correct?
A. Yes.
Q. And the report, the output, will actually list the products that are associated with those reports; correct?
A. In the WHO, yes.
Q. Okay. And did you try to determine how many pseudotumor cerebri reports were listed in connection with other levonorgestrel-based products?
A. No, I did not.
Q. Would it surprise you to learn that if you were to do a search like that, that Norplant and Mirena would have far, far, far more reports than any other levonorgestrel-based product?
MR. SCHMIDT: Objection. Foundation.
THE WITNESS: I don't know if it would surprise me or not.
I think -- I'm unaware of any protective effect from the combination products, so it raises the question of why do some products get reports and others not? And one of the things that we know actually increases the

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reporting rate is actually having an adverse reaction in the labeling, as it is for Norplant.
BY MR. JONES:
Q. But there's no similar adverse reaction for pseudotumor cerebri in the Mirena label; correct?
A. That's correct. And then you have to look at the relative use of the product. So a product could appear to have a large number of reports just by virtue of the fact that it has the majority of the uses of that product.
Q. Can you tell me from your report how many adverse reports there have been made in the FDA FAERS system for Mirena during the life of the product?
A. I don't know if I reported that. That is one of the things in OpenVigil. It doesn't show the whole life of the product because I think OpenVigil goes back to 2004, not all the way back to -- not all the way back to 2000.
MR. JONES: Christina, will you help us find this?
MS. NATALE: Uh-huh.
MR. JONES: It's 76.
THE WITNESS: I mentioned in my report in OpenVigil there are 73,330 reports --
MR. JONES: Okay.

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THE WITNESS: -- associated with Mirena.
BY MR. JONES:
Q. So you used OpenVigil for that calculation?
A. Yes.
Q. And how many reports were there for ParaGard?
A. There are very few reports for ParaGard in that system.
I think that the challenge, and I don't know if it's in my report, but that is the marketing period for ParaGard.
Q. Okay. At Page 44 of your report you say there were 73,330 Adverse Event Reports associated with Mirena; correct?
A. Yes.
Q. And then at Page 45 you say there were 2,266 reports with ParaGard; correct?
A. Yes. But pointing out that --
Q. ParaGard was approved in 1984; correct?
A. Yes, that's right.
I mean, part of the point that I made was that this product had already been on the market for almost 20 years before the OpenVigil database is collecting things, and the older products are known to have far, far fewer reports than the products when they're first on the market.

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Q. How far back does the OpenVigil data go?
A. I believe to 2004.
Q. Is that just that you limited the search to 2004 or is that the oldest data that's available in OpenVigil?
A. That's the oldest data that's available in OpenVigil.
Q. Are you sure about that?
A. No. I'd have to look at their website, but that's what -- as I recall, that's what the numbers are for OpenVigil.
Q. But over the same time period that you searched there were approximately 35 times the number of adverse events reported with Mirena than with ParaGard; correct?
A. Yes. That's not surprising for a new product compared to an old product.
Q. Do you -- Mirena has been on the market in the U.S. for 16 years now; is that correct?
A. Yes, that's correct.
Q. Okay. How many Adverse Event Reports have there been associated with Mirena in the last year?
A. I didn't look that up.
Q. Do you know whether the number of reports, adverse reports, associated with Mirena have gone up or gone down in the last year?

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A. I didn't do that analysis.
Q. Do you know -- you write in your report that Mirena was first approved for marketing in Finland in 1990; is that correct?
A. Yes.
Q. And actually that's not exactly true, is it?
A. Well, I don't know what you mean.
Q. Well, isn't it true that when it was approved, when the product was approved for marketing in Finland in 1990, it was under the name Levonova?
A. I don't recall what the European marketing name was.
Q. Have you ever heard of Levonova before?
A. I may have. I didn't really focus on the marketing of the product before it was approved in the U.S.
Q. At any point during the course of your work in this case have you ever searched to see if there were any pseudotumor cerebri reports in association with Levonova?
A. In the 1990s or you mean still currently?
Q. At any time.
A. I don't know if it's still marketed by that name. But I have -- you know, with -- if it's marketed by Bayer under a different name than Mirena, the reports

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would still come into the AERS database as reports of Mirena adverse experiences, so I would assume that the European reports are actually in the FAERS database.
Q. But you're just assuming that. You don't know.
A. Well, it's -- they're --
MR. SCHMIDT: Object to form.
THE WITNESS: They actually can separate it out by country because Dr. Ross's analysis did the U.S. I tried to see what he was doing and looked at the U.S., Dr. Etminan looked at the worldwide reports, as I recall, and I looked at the total in the world. But I didn't try and separate out European reports.
BY MR. JONES:
Q. So my question is direct. Have you ever sat down at a database and searched to determine whether there were any pseudotumor cerebri reports associated with the usage of Levonova?
MR. SCHMIDT: Object to the preamble. Asked and answered.
THE WITNESS: Not directly. I have searched for the levonorgestrel irrespective of product that would have included Levonova but I did not look for Levonova per se.
BY MR. JONES:
Q. Do you know how many different formulations of

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Mirena there have been since it was first approved as Levonova in Finland in 1990?
MR. SCHMIDT: Objection. Vague.
THE WITNESS: No, I have not tracked the different formulation changes.
BY MR. JONES:
Q. Did you know that the initial studies of the product that were submitted to FDA were based upon formulations different than the formulation that has been marketed in the United States?
MR. SCHMIDT: Object to foundation.
THE WITNESS: I didn't -- I don't recall if I knew that. I focused on the product that was approved in the U.S. and has been used in the U.S.
BY MR. JONES:
Q. The initial IND was submitted to FDA by the Population Council on August 17th, 1983; is that correct?
A. Yes, that is correct.
Q. Okay. And then on November 12th, 1997, the IND was transferred to Berlex Labs, who filed the NDA on January 21st, 2000; is that correct?
A. Yes.
Q. Do you know why there was a 17-year lag between the IND being submitted and the NDA being filed?

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MR. SCHMIDT: Object to characterization.
THE WITNESS: I don't know exactly, but during this time period, the use of IUDs in the U.S. dropped markedly and many, many IUDs were withdrawn from the market after the experience with the Dalkon Shield. So there was a time period here where there was much less interest in the IUD as a contraceptive method than there is today because of that experience.
BY MR. JONES:
Q. Based upon your review of the NDA materials, you realize that Leiras Oy was also involved in seeking approval for Mirena in the United States; correct?
A. I don't recall the exact business relationship between different partners. There were different people -- different companies and different entities involved with the product at different points in time.
Q. You write that FDA approved Mirena on December 6th, 2000, after 41 supplemental submissions; is that correct?
A. Yes.
Q. And did you read all 41 supplemental submissions?
A. No. I read their decision based on the review of that cumulative information.
Q. Did you know that in the period before Mirena

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was approved for use in the United States, that intracranial -- benign intracranial hypertension was added to its investigator brochure?
A. I think I did know that, yes.
Q. Did you know that as far back as the mid-'90s, that benign intracranial hypertension was included as a target diagnosis in a hospitalization study being done by the company?
A. I don't --
MR. SCHMIDT: Object to foundation.
THE WITNESS: I don't recall this. I don't recall that study.
BY MR. JONES:
Q. Were you provided the hospitalization study?
MR. SCHMIDT: Same objection.
THE WITNESS: Not that I recall.
BY MR. JONES:
Q. Have you ever heard of the hospitalization study?
A. Not sitting here today, I don't remember that particular study.
Q. Were you provided with the investigator's brochure?
A. I'm not sure. But I was aware that the investigator's brochure was based on information that

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included information related to Norplant.
Q. Did you know that in the hospitalization study section listing benign intracranial hypertension as a target diagnosis that Bayer said or that the company at that time said that benign intracranial hypertension was known to be related to hormonal contraceptives?
MR. SCHMIDT: Objection. Foundation.
THE WITNESS: I haven't seen that document and I'm not aware that that study actually identified any cases or any study identified cases of benign intracranial hypertension at that time.
BY MR. JONES:
Q. You've given opinions in this case that benign intracranial hypertension/pseudotumor cerebri is not related to hormonal contraceptives; correct?
A. Well, my opinion is specific to Mirena but I also -- I didn't really -- I don't have access to and I don't think -- I don't know if the data -- the documents exist to revisit the entire story with Norplant. But I think with what we know today about Norplant and its follow-on products and pseudotumor cerebri, that that association doesn't meet the current standard for reasonable evidence of causal association, even for Norplant.
Q. Isn't it true that you write in your report that

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benign intracranial hypertension/pseudotumor cerebri is not related to use of hormonal contraceptives?
A. Well, that is my opinion. I think I've focused first on Mirena but, as I just finished up, I also believe that's true about Norplant. And I don't see any evidence that it's related to the oral contraceptives.
Q. Yeah. You talked about -- you said in your report that it's not related to oral contraceptives; right?
A. Yes.
Q. So don't you think that it would have been enlightening to your opinions to know that the company said back in the 1990s that benign intracranial hypertension was known to be related to hormonal contraceptives?
MR. SCHMIDT: I'll object to you asking this line of questions without showing him the document.
MR. JONES: You should have given him the document.
MR. SCHMIDT: We don't need to fight about it.
BY MR. JONES:
Q. You can answer.
MR. SCHMIDT: I don't think it's a fair question, and I'll object.
THE WITNESS: Well, I think that there were risk

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assessments made in the 1990s based on the early Norplant experience that were the state of the knowledge at that time.

What we know now, based on much more extensive use of these products, is that the evidence that was the basis for those opinions in 1990 hasn't been borne out.

So I don't know what my opinion would have been in 1990 and I'm not really offering an opinion about whether the company's opinions were reasonable in 1990 but, as we sit here today, I don't think there is reasonable evidence for a causal association for levonorgestrel and benign intracranial hypertension.

BY MR. JONES:

Q. You talk about 20 investigational trials at Page 21 of your report.

A. Yes.

Q. Can you tell me what formulation of the product was used in those 20 investigational trials?

MR. SCHMIDT: Objection to formulation.

THE WITNESS: Not without going back and reviewing the summary data. But I'm quoting from the summary that the studies that were the basis of the safety database.

BY MR. JONES:

Q. Did you know that the marketed formulation was

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shown in Bayer's studies to actually have higher release rates than the earlier formulations that were used in the pre-approval studies?

MR. SCHMIDT: Object to foundation, characterization.

THE WITNESS: I don't know if that's correct or not. I have not reviewed that information.

BY MR. JONES:

Q. Did you review the NDA package in this case?

MR. SCHMIDT: Asked and answered.

THE WITNESS: Yes, I told you that I reviewed the overall summaries that described the basis for the safety information and the efficacy information. Yes, I did.

BY MR. JONES:

Q. Did you know that the information I've been questioning you about about the different formulations was in the NDA package?

MR. SCHMIDT: Same objection.

THE WITNESS: It wouldn't surprise me. The safety information in an NDA is based on all formulations and all doses that are used during the investigation of the product, so most NDAs will contain safety information about a variety of different doses and exposures and all of that information is considered,

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as is the selection of the product that's going to be marketed.

BY MR. JONES:

Q. You write at Page 24 of your report that IIH most often presents in young women who are overweight or obese, although it is occasionally seen in children, men, and older adults as well; is that correct?

A. Yes.

Q. Okay. And you agree that it's seen in much lesser rates in children, men, and older adults; correct?

A. Yes, that's correct.

Q. Okay. And you agree that PTC/IIH is less common in prepubescent females; correct?

A. Yes, I believe that's correct.

Q. Okay. And doesn't that suggest to you that there's a hormonal component to the development of the disease state?

A. No, not necessarily. There are many differences. There are many diseases which have a predilection for men or for women that are not based on hormonal differences between men and women and differences then in age groups that don't relate to the hormonal changes in ages. So no, I don't think that's direct evidence that it's related to hormonal changes.

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Q. You talk about signs and symptoms of IIH/PTC include papilledema, headache, pulsatile noises, and visual disturbances; is that correct?

A. Yes.

Q. And did you review all Bayer Adverse Event Reports that included these terms?

A. No, I did not.

Q. You mentioned earlier in your experience at one of your pharmaceutical companies that you were familiar with a software system called Argus?

A. Yes.

Q. Were you given access to Bayer's Argus system to perform searches for this case?

A. No, I didn't feel that was necessary for me to develop my opinions.

Q. You don't contend that obesity causes pseudotumor cerebri, do you?

A. I would describe that as a causal association. It's -- it -- there could be something about obesity and about the changes in the body associated with obesity that is the underlying cause but I don't think the mechanism is actually well understood.

Q. Is that something that happens in the body, is it hormonal?

A. No, there's things that happen in the body that

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aren't hormonal.
Q. What percentage of obese or overweight women develop PTC?
A. Well, I think the rates that -- you know, the rates in the general population are thought to be one to two per hundred thousand and the rates in obese women of childbearing potential are as high as 20 per hundred thousand.
Q. So a very small percentage of women of childbearing age who are overweight or obese ultimately develop PTC; correct?
A. Yes, that's correct.
Q. But you believe there's a causal association between obesity and overweight and PTC?
A. Yes. When we say the word "association," it means causation hasn't been proven, but that gives you a risk factor that increases the risk, you know, 10- to 20-fold. That's greater than the risk of cigarettes for lung cancer.
Q. Let's talk about cigarettes and lung cancer.
Is there an established pattern of development of lung cancer with cigarette smokers?
A. Well, I think the epidemiology is well stood, if that -- understood, if that's what you mean by pattern, yes.

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Q. No. I'm talking about a temporal pattern.
A. Well, the temporal relationship is that smokers' risk increases steadily with duration of use, which is temporal, and also amount of use.
Q. Some cigarette smokers never develop lung cancer; right?
A. That's correct.
Q. Okay. I'm a cigarette smoker. Can you tell me as we sit here today, based upon current scientific knowledge, when or if I will develop lung cancer?
A. No. It's -- the smoker's risk of lung cancer -- the average smoker's risk of lung cancer is approximately ten times greater than the risk of a non-smoker.
Q. But the inability to determine a time period in which someone will develop lung cancer does not negate the fact that there is a causal association between smoking cigarettes and lung cancer; correct?
A. Well, that's correct. For any given individual you can't predict what will happen.
Risk changes over time, risk changes with dose. There's many different sources of evidence that suggest that cigarettes and lung cancer is a causal association. But not every lung -- not every smoker gets lung cancer, it's just that the risk is much higher if you're a

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smoker.
Q. And if I get lung cancer, stopping smoking is not going to make the lung cancer go away, is it?
A. In the case of lung cancer, stopping smoking will not make it go away. That's correct.
Q. You say that at Page 24, due to increases in obesity, since those data were generated several decades ago and because obesity has dramatic -- because obesity dramatically increases the risk for IIH, the incidence rate is likely higher today.
Did I read that correctly?
A. Yes.
Q. Okay. And can you point me to any scientific studies anywhere that show that the incidence rate of PTC is higher today because of increases in obesity?
A. No. It's an indirect conclusion. We know the obesity -- proportion of the population that's obese is higher than it's been in the past and we know that obesity, the prevalence in obesity is higher; therefore, the prevalence in the population which has more obesity will have a higher prevalence.
Q. What percentage of the U.S. population is obese or overweight?
A. Obese or overweight, overweight is usually defined with a BMI of 25 and obese at 30 and more

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serious obesity at a BMI of 35.
Actually, I don't remember the exact number. I know the number that is overweight or obese is more than half the population.
Q. And I've seen it referred to as about two-thirds.
A. Yes, that probably is correct.
Q. Okay. And do you know what percentage of Mirena users would be considered overweight or obese?
A. No, I do not.
Q. You've never seen any data on that point?
A. I don't know if it's available, but I don't recall seeing estimates of obesity in Mirena users.
Q. Have you ever asked Bayer's lawyers for that data, the obesity and overweight percentage of its users?
A. No. I think that the thing I was trying to determine was the obesity in the cases that are reported with PTC, but I didn't ask for it for the Mirena users.
Q. At Page 25 you say, with many patients, IIH either resolves spontaneously or resolves after the patient receives a lumbar puncture.
Did I read that correctly?
A. Yes.
Q. And do you know what percentage of patients have

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spontaneous resolution of their IIH?
A. No, I don't.
Q. Do you know scientifically the reason why one would experience spontaneous resolution of IIH?
A. No. I know it's a situation -- it's a -- it's one of the conditions that waxes and wanes and sometimes recurs but I don't know if we know the reasons for why it can spontaneously resolve without treatment.
Q. And it resolves sometimes after a patient receives a lumbar puncture, which is a diagnostic tool for determining whether one has PTC; correct?
A. That's correct.
Q. Does it completely resolve in those patients or does it sometimes just provide temporary relief?
A. I think it's variable.
Q. And you would agree with me, wouldn't you, that there are patients who have developed PTC that will have it permanently, regardless of whether their -- they lose weight or not?
MR. SCHMIDT: Objection. Vague.
THE WITNESS: I'm not sure what you mean by permanently. There are neurologic complications in some patients that are permanent, that persist, so in that sense, the condition can have permanent effects, yes.

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BY MR. JONES:
Q. Are you aware of any cure for PTC?
A. Well, I guess I don't think of it as a disease that has a cure or not a cure. It has treatments that resolve, resolve the episode, which, you know, include lumbar puncture and acetazolamide, which is a diuretic, and, as I mentioned, some -- you know, some patients will spontaneously improve, others will have recurrences.
Q. The treatments resolve the symptoms; correct?
A. Yes.
Q. There's no pill that you can take that just cures you of the disease.
A. Well, I'm not sure I understand the distinction. I guess I don't think of this as necessarily a chronic, persistent condition of -- I think there are many patients where the episode resolves and does not recur.
Q. And, alternatively, there are many patients where the condition does not resolve; correct?
A. There are some. I don't know the breakdown.
Q. Because you're not -- you said earlier --
A. I'm --
Q. -- you're not an expert on PTC/IIH; correct?
A. No, I'm not offering -- I'm not offering an

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opinion about that.
I can recall in the case-controlled studies, in one case-controlled study where they identified patients, approximately half of them were patients with recurrences and the other half had never had a recurrence after the resolution. But I don't know if that's representative.
Q. You mentioned that -- oh, strike that.
At Page 25 you talk about the IIH warning was added to Norplant based on a small number of case reports?
A. Yes.
Q. Okay. How many is a small number?
A. Well, I think I walk through in Section 1, which begins on the bottom of 26, the evidence, beginning with two reports and then in 1995 two additional reports and then reports by Alder, who identified 56 cases, although it's not clear that they're all IIH because he included disk edema alone, which may or may not have been -- may not have been pseudotumor cerebri. But these were the cases that resulted in the Norplant warning.
Q. Do you know when the Norplant warning was added to the label?
A. 1992, I believe.
Q. Okay. And you were just talking about, I asked

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you about the small number of case reports and you were citing to 1995 articles; right?
A. Well, that's right. I think there were much fewer than that. So initially, it was based on a very small number.
Q. Well, you say "much fewer than that."
Can you point me to any evidence anywhere that tells me exactly how many number of case reports were in Wyeth's possession at the time that it proposed the labeling change to add idiopathic intracranial hypertension to the Norplant System?
A. I don't have any data that actually indicates the number of reports.
We know that by the time of the Alder report in '95, that Wyeth-Ayerst commented that they had 70 reports by 1995. And, of course, by that time, it's in the labeling and attention is being called to it. But I actually don't have the historical data of how many cases were initially reported.
Q. And so when you say small, that it was based on a small number of case reports, where are you getting that information that it was a small number versus a large number?
A. Well, the fact that even by '95, we're still dealing with -- you know, after the condition has been

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publicized, we're still dealing with, at most, the 70 cases and the cases at the time of the labeling had to be some smaller set of that 70.
Q. Okay. Because it was changed three years earlier.
A. Yes, that's right.
Q. So you're concluding that it was something substantially less than 70 when Wyeth proposed this labeling change; right?
A. Yes.
MR. SCHMIDT: Object to characterization.
THE WITNESS: Well, and there's nothing in the literature that describes a larger number of cases.
BY MR. JONES:
Q. And today you're aware that there are well over 100 cases of PTC/IIH reported in association with Mirena; right?
A. Yes, that's correct.
Q. Okay. And you're not aware of any efforts by Bayer to go to the FDA and propose a labeling change to add IIH/PTC; correct?
A. Well, that's correct.
I think those are the number of cases that have been acquired over all of the use since the product has been on the market and reflects a very different

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situation than the labeling decisions that were made when Norplant was relatively new to the market.
Q. Okay. Let's look at, you cite the label change starting at Page 25 and going to Page 26. Okay?
A. Yes.
Q. And it says, "Idiopathic Intracranial Hypertension," and then beginning with the first sentence, idiopathic intracranial hypertension (pseudotumor cerebri, benign intracranial hypertension) is a disorder of unknown etiology which is seen most commonly in obese females of reproductive age.
Do you agree with that?
A. Yes, you read that correctly.
Q. Okay. Do you agree with that statement, though?
A. Yes.
Q. Okay. There have been reports of intracranial hypertension -- there have been reports of idiopathic intracranial hypertension in Norplant System users.
Do you agree with that?
A. Yes, there were reports.
Q. Okay. And do you agree that, as we sit here today, there have been reports of idiopathic intracranial hypertension in Mirena users?
A. Yes, that's also correct.
Q. Okay. And you would agree that going all the

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way back to 2002, there had been reports of idiopathic intracranial hypertension in Norplant System users.
A. Yes, that's correct.
Q. A cardinal sign of idiopathic intracranial hypertension is papilledema. Early symptoms may include headache associated with a change in frequency, pattern, severity or persistence. Of particular importance are those headaches that are unremitting in nature and visual disturbances.
Do you agree with that?
A. Yes, I think that's correct.
Q. Okay. Patients with these symptoms, particularly obese patients or those with recent weight gain, should be screened for papilledema and, if present, the patient should be referred to a neurologist for further diagnosis and care.
Do you agree with that?
A. Yes, generally.
Q. What do you not agree with in that sentence?
A. I think it's just a matter of medical judgment when you screen a patient for papilledema. Many of these symptoms are nonspecific and so it would really depend on the patient's history. But, generally speaking, I think that's reasonable advice.
Q. Yeah. It's not wrong to tell doctors that if

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you see these symptoms in your patients, particularly obese patients or those with recent weight gain, to screen them for a serious condition. That's not unreasonable, is it?
A. No, it's not unreasonable.
Q. And then the final part of the Norplant label says, Norplant System should be removed from patients experiencing this disorder.
Do you agree with that?
A. Well, that's what the statement says. I -- in hindsight, looking back at that, we know now that the IIH resolves in patients when you leave it in and there's other patients when you take it out and they're given other treatments, it resolves in them as well. It's not clear to me, sitting here today, that that is still a well-founded recommendation.
Q. If you had a patient come to you that had PTC/IIH that had the Norplant System in there, would you recommend removal?
MR. SCHMIDT: Objection. Foundation, incomplete hypothetical.
THE WITNESS: I think it would -- this was information that was written almost 25 years ago.
I think with what we know now, I think it would be an individual discussion with the patient and it

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might be very reasonable to treat the patient and see if the symptoms resolve.
BY MR. JONES:
Q. What do we know now that makes it safe to leave a Norplant System in a patient who's experiencing PTC?
MR. SCHMIDT: Object to characterization.
THE WITNESS: Well, what we know now is that the sparsity of reports, despite 30 years of use and millions and millions of patients of use, is that, you know, based on this initial prediction, had it been correct, this should have been an ongoing and, you know, management problem with patients taking levonorgestrel and yet for the products that come out further -- I mean, you see this if you just even look at the U.S. reports in the OpenVigil database system. We have 24 reports in ten years of experience and we have reports of patients whose symptoms resolve when the Mirena is not removed.
So I think that's a little categorical and I think it's an individual decision that should be made between the patient and the physician.
BY MR. JONES:
Q. You read the literature that you cited about Norplant, the Norplant experience; correct?
A. Yes.

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Q. And you agree with me that in that, in that literature, the Wysowski article, the Oliver letter, those cite to patients that the symptoms went away when the Norplant was removed; right?
A. Yes. But we know now that when Mirena is left in place, which is, you know, another source of levonorgestrel, that the patients will often improve even when it's left in place.
Q. More often -- if you've looked at the documents, more often, isn't it true that patients actually have a resolution of symptoms after the Mirena is removed?
MR. SCHMIDT: Object to foundation.
THE WITNESS: Well, again, there are very few patients you can interpret that that's due to the Mirena removal because that's not all that's done. They're also treated with lumbar punctures and with diuretics.
So my interpretation of the evidence is that the symptoms resolve whether you remove the Mirena or not.
MR. JONES: Okay. We have to take a break. We'll pick back up there when we come back.
VIDEO OPERATOR: This is the end of Media Number 3.
We are going off the record at 4:54 p.m.
(Recess, 4:54-5:05 p.m.)
VIDEO OPERATOR: This is the beginning of Media

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Number 4.
We are back on the record at 5:05 p.m.
BY MR. JONES:
Q. Dr. Ellman (sic), we're back on the record.
Can you go to Page 41 of your report.
A. Okay.
Q. Okay. The first full paragraph, third sentence, you say, Bayer reasonably and appropriately decided that the Norplant label should be used only on a case-by-case basis when scientific evidence demonstrated its applicability to Mirena, and then there's a Footnote 69.
Do you see that?
A. Yes.
Q. Okay. And then if you go down to Footnote 69, the label on the document is MIR_JR_00186491.
Did I read that correctly?
A. Yes.
Q. Okay.
MR. JONES: I'm going to hand this to the court reporter to be marked as Deposition Exhibit 7.
(Exhibit Feigal-7 was marked for identification.)
BY MR. JONES:
Q. Is the document that I handed you, on the front page does that say MIR_JR_00186491?

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A. Yes, it does.
Q. Okay. And is that the document cited in Footnote 69 of your report?
A. Yes.
Q. Okay. And can you point me to where in this document it mentions Norplant?
MR. SCHMIDT: I'll object to the premise of this question.
MR. JONES: Can you be more specific? Maybe I can fix it.
MR. SCHMIDT: Yeah. I think you're citing the wrong document from his report.
MR. JONES: And why do you say that?
MR. SCHMIDT: Because I think what he's using for the Norplant proposition is 70.
MR. JONES: It cites Footnote 69 for the sentence that I read.
THE WITNESS: Well, I think this is the document that lays out the labeling strategy and then 70 I think is a quote from a Bayer document where it's discussing a risk factor that is in Norplant.
BY MR. JONES:
Q. Well, let's read your sentence again: Bayer reasonably and appropriately decided that the Norplant label should be used only on a case-by-case basis when

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scientific evidence demonstrated its applicability to Mirena, Footnote 69; correct?
A. Yes.
Q. Okay. So tell me where in this document it mentions the word "Mirena."
MR. SCHMIDT: Same objection.
THE WITNESS: Oh. Well, I think you meant Norplant.
MR. JONES: Or Norplant.
THE WITNESS: Yes.
It does not. These two sentences go together and the two footnotes and the two documents go together.
So the first document lays out the labeling team and the strategy and shows the deliberate way in which they were approaching the labeling and then Document 70 is actually a specific reference to a Norplant warning that they're considering for Mirena.
BY MR. JONES:
Q. Well, isn't conventional use of a citation something to support the proposition that you've just laid out in the sentence that you're citing to?
A. Yes.
MR. SCHMIDT: Objection.
BY MR. JONES:
Q. Can you -- do you see -- can you flip to

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MIR_JR_00186492.
MR. SCHMIDT: Can you give me that number again?
MR. JONES: MIR_JR_00186492.
MR. SCHMIDT: Thank you.
MR. JONES: The second page of the document, on the back side.
THE WITNESS: Oh, okay.
MR. JONES: Okay.
BY MR. JONES:
Q. Do you see down towards the bottom where it says, it was proposed to follow the, redacted other Bayer, label with respect to, and then it lists some items?
A. Yes.
Q. Okay. Were you ever provided with a copy of a document that did not have that redacted other Bayer box over whatever the text is underneath that?
A. Not that I recall.
Q. Were you -- see on the next page it says, "Redacted: Manufacturing/CM&C"?
A. Yes.
Q. Okay. And were you ever provided a copy of this document without the redactions for Manufacturing/CM&C redaction?
A. No; although I don't think the chemistry,

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manufacturing and controls are relevant to what I was reviewing.
But I think the document does show that they're taking labeling from other labeling, and then when you look at the other document where I have a direct quote, you can see that it does relate to Norplant.
Q. I just wanted to make sure you were -- you're not using this document to say that Bayer reasonably and appropriately decided that the Norplant label should be used only on a case-by-case basis when scientific evidence demonstrated its applicability to Mirena.
MR. SCHMIDT: Object to characterization.
THE WITNESS: Well, I think the document does show. I mean, the product is redacted, but if you look at the other document and we trace it back to Norplant, they are basing it on another label, and that's what this document shows and that's what I've said in that sentence.
BY MR. JONES:
Q. So are you concluding that this redaction and the it was proposed to follow the redacted label with respect to, are you concluding that it says Norplant under that redaction box?
A. As I recall -- I don't have the other document in front of me, but the other document is a specific

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example of a Norplant issue that they are looking at and it's an example of their case-by-case examination of the Norplant warnings and not just -- and issues in Norplant and not just accepting or rejecting all of them. They're making their decisions on a scientific basis.
Q. Let's switch gears a little bit.
Back when you were at FDA, did you feel as though FDA had adequate resources to do its job and satisfy its mission?
A. For the most part. There were some areas, particularly foreign inspections, where FDA could have used additional resources and, to an extent, even for some domestic, domestic inspections. But at the review divisions I felt, that I was responsible for, that I had adequate resources.
Q. Do you feel as though, is it your belief that FDA has adequate resources today to meet its mission?
A. I think if the word is "adequate," yes. I think actually there are areas still where there are needs to -- needs -- where there's a need to add specific types of scientists and reviewers. So it's an ongoing process of building and improving the FDA but I think that from a -- the issues that are relevant to this case, the FDA resources are adequate, and it's actually where FDA places in the drug center a large percentage

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of its resources is in the review process.
Q. Based upon your experience at FDA, did you ever feel as though there was a lack of adequate resources that rose to the level of being a crisis for the FDA?
A. No.
Q. Do you remember being involved in an American course on drug development and regulatory sciences at the Mission Bay Conference Center at UCSF?
A. Yes.
Q. Okay. And your wife also -- you were a faculty member at that conference; correct?
A. That's right. My wife was the course director, and I still teach in that -- that course is still ongoing. It's jointly taught by FDA and UC-San Francisco. And actually, there's a session next week where I'm giving two lectures.
Q. Okay. And you were involved in a section called "The Global Registration and Approval Process"; correct?
A. I don't recognize that title but --
Q. Okay. Well, let me try to refresh your recollection.
A. Okay.
Q. Some of the lectures given as part of that were the history of regulation of drugs and biologics, U.S., U.K., Germany, and Japan, FDA regulatory pathways, INDs,

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EINDs, NDAs, BLAs, 505 B1, 505 B2, and ANDAs, EMA and EU registration procedures, centralized procedure, mutual recognition procedure, and decentralized procedure. There were also presentations on FDA's critical path initiative.
Have you ever heard of that before?
A. Yes, I was there when that program was implemented and designed.
Q. Okay. There were also presentations on the IOM report on drug safety and FDA Science Board Subcommittee on Science and Technology Report, "FDA Science and Mission At Risk. Where Are We Now?"
Do you remember that?
A. Yes, I know that report. Yes.
Q. And do you know the report, the FDA Science and Mission At Risk report?
A. Yes, I know that report.
Q. Okay. And can you tell me what the FDA Science and Mission, FDA Science and Mission At Risk report is?
A. This was a report prepared by the FDA Science Board. I was actually a member of that board while I was the center director because the center directors sit on that board with some external advisors.
It was a report prepared at the request of the FDA as part of a budget justification for increasing

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staffing in some areas, for improving computer systems. There's other areas. Those are just a couple that I recall that were identified in the report.
MR. JONES: Can we mark that as Deposition Exhibit 8.
(Exhibit Feigal-8 was marked for identification.)
BY MR. JONES:
Q. What's been handed to you is the FDA Science and Mission at Risk report of the Subcommittee on Science and Technology prepared for the FDA Science Board dated November 2007; is that correct?
A. Yes.
Q. And you've seen this report before; right?
A. I have.
Q. Okay. And let's go, can we flip over to the -- it's the fourth page in that set but it's labeled little I, little I, little I.
A. Oh, okay.
Q. See where it says "FDA Mission Statement"?
A. Yes.
Q. Okay. It reads, the FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food

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supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
Did I read that correctly?
A. Yes, you did.
Q. And did you understand that to be FDA's mission?
A. That is FDA's mission statement, yes.
Q. Okay. And let's flip over to the next page where it says "Executive Summary."
A. Yes.
Q. Second paragraph, a strong -- or first paragraph, a strong Food and Drug Administration is crucial for the health of our country.
Do you agree with that?
A. Yes.
Q. Second paragraph, the FDA constitutes a critical component of our nation's healthcare delivery and public health system.
Do you agree with that?
A. Yes.
Q. The FDA, as much as any public or private sector

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institution in this country, touches the lives, health, and well-being of all Americans and is integral to the nation's economy and its security.

Do you agree with that?

A. Yes, I do.

Q. Okay. Going down to the fourth paragraph, the FDA is also central to the economic health of the nation, regulating approximately $1 trillion in consumer products or 25 cents of every consumer dollar expended in this country annually.

Do you agree with that?

A. Yes.

Q. Go to the next page. It begins, thus, the nation is at risk if FDA science is at risk.

Do you agree that the nation is at risk if FDA science is at risk?

A. Generally speaking, that's true. I think you have to get much more specific.

And, in fact, when you look at the risks they're talking about, they lead off with the need to improve the science in the food science area and food safety because there's approximately 50,000 deaths a year from food poisoning and food contamination.

So there are very specific examples that are given in the report. I think you need to look at the

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report examples rather than to --

Q. But --

A. -- accept the broad premise that the nation is at -- that all parts of things that FDA regulate are at risk because some things need resources and other things are in pretty good shape.

Q. Well, and that's what we're doing. We're going to look at the report.

A. Okay.

Q. But you agree with me that this report is not limited to food safety, is it?

A. Oh, no, it's not.

Q. And --

A. It's all FDA products.

Q. It relates to drugs that are regulated by the FDA; correct?

A. Yes.

Q. And combination products that are regulated by the FDA; correct?

A. Yes, that's correct.

Q. Okay. Let's go over to or let's go down. It says, the Subcommittee concluded that science at the FDA is in a precarious position. The agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities.

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Did I read that correctly?

A. You did read it correctly.

Q. Okay. The Subcommittee found that the deficiency has two sources: The demands on the FDA have soared due to the extraordinary advance of scientific discoveries, the complexity of the new products, and claims submitted to FDA for premarket review and approval, the emergence of challenging safety problems, and the globalization of the industries that FDA regulates.

Did I read that correctly?

A. Yes, you did.

Q. And next it reads, the resources have not increased in proportion to the demands. The result is that the scientific demands on the agency far exceed its capacity to respond. The imbalance is imposing a significant risk to the integrity of the food, drug, cosmetic, and device regulatory system and, hence, the safety of the public.

Did I read that correctly?

A. Yes, you did.

Q. Okay. Let's go to the next page, "1.2 Major Findings."

Do you read -- see that?

A. Yes.

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Q. Okay. Below that, the Subcommittee found substantial weaknesses across the agency, with the possible exception of some drug and medical device review functions funded by our industry fees. There are several areas of greatest concern, however, which form the basis for this report's most significant findings.

Did I read that correctly?

A. Yes.

Q. Okay. And below that, the FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak.

Did I read that correctly?

A. Yes, you did.

Q. Going down into the box, it says, FDA's inability to keep up with scientific advances means that American lives are at risk.

Did I read that correctly?

A. Yes, you did.

Q. Going to the last sentence, likewise, evaluation methods have not kept pace with major advances in medical devices and uses of products in combination.

Did I read that correctly?

A. Yes. And on the next page they give an example of the products they're talking about.

Q. And we talked earlier, Mirena is a combination

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product, isn't it?
A. Yes, it's --
MR. SCHMIDT: Asked and answered.
THE WITNESS: Yes, it's a medical, it's a medical device that's a drug delivery device so it's a combination device and drug.
MR. JONES: Okay.
BY MR. JONES:
Q. And then down below that it says, the world looks to FDA as a leader to integrate emerging understanding of the biology of medicine, technology, and computational mathematics in ways that will lead to successful disease therapies. Today, not only can the agency not lead, it cannot even keep up with the advances in science.
Did I read that correctly?
A. You did.
I don't think I agree with that conclusion by the Committee, but they're entitled to their opinion.
Q. Sure.
Let's go to the next page. Due to constrained resources and lack of adequate staff, FDA is engaged in reactive regulatory priority setting or a fire-fighting regulatory posture instead of pursuing a culture of proactive regulatory science.

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Did I read that correctly?
A. Yes. And they point out they're talking about the Center for Food and the Center for Veterinary Medicine.
Q. Actually, what they say is that is particularly true for those two entities; correct?
A. Yes.
Q. Okay. The FDA cannot adequately monitor the -- monitor development of food and medical products because it is unable to keep up with scientific advances.
Did I read that correctly?
A. Yes. And then they list the advances, and you can see that none of those really apply to Mirena.
Q. The next sentence then -- we'll see what the document says.
The Subcommittee identified the following emerging -- eight emerging science and technologies that are most challenging the FDA: Systems biology, including genomics and other -omics, wireless health-care devices, nanotechnology, medical imaging, robotics, cell- and tissue-based products, regenerative medicine, and combination products.
Did I read that correctly?
A. You did.
Q. Each of these emerging areas is developing at an

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exponential rate and each generates novel scientific, analytic, laboratory, and/or information requirements.
Did I read that correctly?
A. Yes, you read that.
Q. Next sentence, the FDA cannot fulfill its surveillance mission because of inadequate staff and IT resources to implement cutting-edge approaches to modeling, risk assessment, and data analysis.
Did I read that correctly?
A. Yes.
Q. The FDA lacks a coherent scientific structure and vision as a result of weak organizational infrastructure.
Did I read that correctly?
A. You did.
Q. Last sentence, consistent and rigorous peer reviews of programs and processes which are currently lacking are critical for wise utilization of resources and for rebuilding the agency's ability to implement its science-based regulatory responsibilities effectively.
Did I read that correctly?
A. Yes, you did.
Q. Next, the FDA cannot fulfill its mission because its scientific workforce does not have sufficient capacity and capability.

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Did I read that correctly?
A. Yes, you did.
Q. The Subcommittee found that, despite the significant increase in workload during the past two decades, in 2007 the number of appropriate -- number of appropriated personnel remained essentially the same, resulting in major gaps of scientific expertise in key areas.
Did I read that correctly?
A. Yes.
And the word "appropriated" is very important because the size of the FDA by 2007 had nearly doubled, its budget now has quadrupled because of the user fees. So while the congressional appropriated, funded staff or funds for staff remains constant -- and this is a document prepared with Congress in mind -- the FDA has actually been adding the staff in these areas based on user fees.
Q. But as of 2007, this was the Committee's report; correct?
A. Well, it's about the appropriated rather than -- it's not talking about the total FDA workforce, they're talking about the congressional appropriation, which had remained relatively flat at right around 10,000, you know, 10,000 employees, but -- and the budget, the

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appropriated budget, had remained relatively flat, right around a billion dollars, but by 2007, as I recall, it was almost an additional billion dollars from user fees that provided staff. In fact, more than half the staff in the review divisions are funded by other sources than appropriated dollars.
Q. Okay. More importantly, despite the critical need for a highly trained workforce to fulfill its mission, the FDA faces substantial recruitment and retention challenges.
Did I read that correctly?
A. Yes. That's true of some parts of FDA.
Q. But it doesn't say some parts of FDA in the document, does it?
A. No. But I know -- I mean, I know what parts of FDA that have problems and other areas -- you know, in the device center the average tenure of my thousand staff was 17 years, so we had a 3 percent turnover rate.
So the document is very -- speaks in the introduction in very broad terms. You actually have to sort of drill down and see the specific areas they're talking about.
Q. There's insufficient investment in professional development, which means that the workforce does not keep up with scientific advances.

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Did I read that correctly?
A. You did.
Q. Okay.
A. And, again, it's very -- it varies from organizational unit to organizational unit.
Q. FDA's failure to retain and motivate its workforce puts FDA's mission at risk. Inadequately trained scientists are generally risk-averse and tend to give no decision, a slow decision or, even worse, the wrong decision on regulatory approval or disapproval.
During our encounters with staff and center leadership, we were struck by the near unanimity at the shortage of science staff due to the lack of resources to hire and the inability to recruit and retain needed expertise are serious, long-standing challenges. Internal expertise and experience to provide the science capability and capacity needed in highly specialized and fast-evolving areas is disturbingly limited.
The lack of a trained workforce means that the FDA is ineffective in responding to emerging fields that require individuals and work teams with multi-disciplinary skills built on very complex, highly specialized, and often esoteric bodies of knowledge.
Did I read that correctly?
A. Yes, you did.

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Q. Going down, the FDA was extremely disturbed at the state of the FDA IT infrastructure.
Did I read that correctly?
A. Yes, you did.
Q. It also found that the FDA has insufficient access to data and cannot effectively regulate products based on new science due to lack of supportive IT infrastructure.
Did I read that correctly?
A. Yes, you did.
Q. Okay. The IT situation at FDA is problematic, at best, and, at worst, it is dangerous. Many of the FDA's systems reside on technology that has been in service beyond the useful life cycle. Systems fail frequently, and even E-mail systems are unstable, most recently, during an E-Coli food contamination investigation. More importantly, reports of product dangers are not rapidly compared and analyzed.
Did I read that correctly?
A. Yes. This is a good description of the Food Center.
Q. It doesn't say the Food Center there, does it, sir?
A. Well, the E-Coli --
MR. SCHMIDT: Object to characterization.

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THE WITNESS: The E-Coli food contamination, their one example that they give, is a Food Center issue.
BY MR. JONES:
Q. But, sir, this paragraph does not refer to the Food Center, does it?
MR. SCHMIDT: Objection. Asked and answered, argumentative.
THE WITNESS: This is an overall statement, but the examples that they're citing are -- throughout most of this report are in the Center for Food and the Center for Veterinary Medicine, two of the centers that in 2007 had no user fee resources compared to the Drug Center, which by this time had more than doubled in size over the last decade.
MR. JONES: Move to strike as nonresponsive.
MR. SCHMIDT: I'll object to that motion.
BY MR. JONES:
Q. Reading, critical data reside in large warehouses sequestered in piles and piles of paper documents. There's no backup of these records, which include valuable clinical trial data.
Did I read that correctly?
A. You did, yes.
Q. The FDA has inadequate extramural funding

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programs and collaborations to accelerate the development of critical health information exchanges in order to support clinical trials and pharmacovigilance activities.

Did I read that correctly?

A. Yes, you did.

Q. And there are no pharmacovigilance activities associated with food, is there?

A. Well, they're not pharmacovigilance but there's food safety vigilance programs, yes.

Q. That's right. And that's in that paragraph that you were trying to say related to food safety; correct?

MR. SCHMIDT: Objection. Argumentative.

THE WITNESS: No. They give examples, they do give examples from drugs, although not very many.

MR. JONES: Okay.

BY MR. JONES:

Q. The next, 1.3, at the bottom, in contrast to previous reviews that warned crises would arise -- would arise if funding issues were not addressed, recent events in our findings indicate that some of those crises are now realities and American lives are at risk.

Did I read that correctly?

A. Yes, you did.

Q. Going to the next page, we found that FDA's

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resource shortfalls have resulted in a plethora of inadequacies that threaten our society, including, but not limited to, inadequate inspections of manufacturers, a dearth of scientists who understand emerging new technologies, inability to speed the development of new therapies, an import system that is badly broken, a food supply that grows riskier each year, and an information infrastructure that was identified as a source of risk in every center and program reviewed by the Subcommittee. We conclude that FDA can no longer fulfill its mission without substantial and sustained additional appropriations.

Did I read that correctly?

A. Yes, you did.

Q. Although there is indeed great urgency to stem the tide of continued deterioration and the science that supports the regulatory decisions of the FDA, the magnitude of changes that are needed will require a phased approach based on a well-thought-out plan.

Did I read that correctly?

A. Yes.

Q. For example, during the time of our review, the directorship of two of the largest FDA centers, CFSAN and the Center for Drug Evaluation and Research, became vacant. It will be difficult, if not impossible, to

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recruit the best leaders unless there is assurance that adequate resources and staff will be available to address the challenges.

Did I read that correctly?

A. Yes, you did.

And the Center for Drug position was filled immediately. That person remains in that job and she's held that job since 1993, with a brief time when she worked in the commissioner's office. So they predicted that it would be a problem but, in fact, it was not.

Q. Not according to this report.

The magnitude of the resources --

MR. SCHMIDT: Object to -- objection.

Just a second.

Objection. Argumentative.

BY MR. JONES:

Q. The magnitude of the resources required to restore scientific capability and capacity is substantial.

Did I read that correctly?

A. Yes.

Q. We recognize -- next page. We recognize that adequate resources, human and financial, alone will not be sufficient to repair the deteriorating state of science at FDA, which is why we also recommend

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significant restructuring. But without a substantial increase in resources, the agency is powerless to improve its performance and will fall further behind and will be unable to meet either the mandates of Congress or the expectations of the American public.

Did I read that correctly?

A. Yes, you did.

Q. Okay. Let's go down to, it's Page 11, and you see a chart there. Let's go to the section that talks about the Center for Drug Evaluation and Research, the CDER.

Are you with me?

A. Yes.

Q. Okay. CDER regulates the safety, efficacy, quality, and advertising of all drug products marketed in the U.S., including brand-name and generic pharmaceuticals, over-the-counter medicines, therapeutic proteins --

And can you help me out with that word? Mono?

A. Monoclonal antibodies.

Q. Oh.

-- monoclonal antibodies, 2,500 U.S. and 2,500 foreign non-gas manufacturers, 5,000 active commercial Investigational New Drug Applications, 12,000 drug products, 3.3 billion prescriptions per year, 61,000

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pieces of promotional material received for review, 290 billion in pharmaceutical sales, brand prescription sales 221 billion, generic prescription sales 54 billion, and over-the-counter sales 15 billion.

Did I read that correctly?

A. Yes.

Q. Okay. Let's go to Page 12.

Science forms the basis of all regulatory decisions. Those --

MR. SCHMIDT: Where are you reading from?

MR. JONES: The last sentence.

BY MR. JONES:

Q. Science forms the basis of all regulatory decisions. Those that do not have adequate scientific support are thus subject to delays or, worse, poor decisions. Therefore, effective regulation requires that the scientific competency within FDA matches or exceeds an applicant's knowledge.

Did I read that correctly?

A. Yes.

Q. Next page, first paragraph, last sentence, the bulk of the agency's activities involve reviewing new drugs, biologics, medical devices, and additives. It is clear from this list that the FDA must master science at the molecular and nanoscale and be able to detect,

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assess, and respond to the growing risks resulting from globalization.

Did I read that correctly?

A. Yes.

It's referring back to the description of genomics and nanotechnology, which in 2007 -- genomics has actually come -- has actually become important, nanotechnology not so much.

Q. Okay.

A. So they're anticipating these would be new areas that the center would need to -- the centers would need to deal with.

Q. Next paragraph towards the bottom, an even broader range of activities related to surveillance of adverse events is needed with marketed products: Surveillance and efficacy and safety assessments need support. These iterative and complex activities consist of multiple sublevels of activity, such as science-based interactions with third parties. Surveillance also requires an array of analytic activities as well as extensive risk communications activities.

FDA must have the scientific staff and resources to undertake the regulatory research that will provide a basis to, one, improve capacity for safety and efficacy evaluations and monitoring of candidate and licensed

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products; two, modernize current regulatory pathways; and, three, develop new regulatory pathways where there are currently none. Much of this research must be undertaken by FDA because it is mission critical and because it either cannot or will not be done by other government agencies or industry.

Did I read that correctly?

A. Yes, you did.

Q. Okay. Next page, second paragraph, in summary, getting the science right is critical to FDA's ability to fulfill its mission. Decisions made in regulation development, premarket approvals, legal actions, and related public health emergencies must be based on understanding of contemporary and emerging science within the context of the risk analysis paradigm.

Did I read that correctly?

A. I lost where you were. Oh, I see where you are.

Yeah, what you did is you just skipped over several paragraphs where they cited examples where FDA had actually done a good job.

Q. Well, I'll let your counsel go into that because I only have so much time with you.

Next page, Center for -- the chart, Center for Drug Evaluation and Research, CDER, premarket reviewed and approved 101 prescription drugs and biologics, 14

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OTC medications, 371 generic drugs, and conducted 648 clinical research inspections.

That was for 2000 -- fiscal year 2006; correct?

A. Yes, that's right.

Q. Okay. And then post-market, fiscal year 2006, received 471,000 AERS reports.

Those are Adverse Event Reports; correct?

A. Yes, that's right.

Q. Issued 16 public health advisories, reviewed 13,000 medication error reports, issued 70 drug promotion violation letters and 530 advisory letters.

Product quality, reviewed 184 pre-approval inspections in support of 81 new drugs and 109 generic applications, reviewed 1,329 cGMP inspections, received 2,670 Drug Quality Reports, and coordinated 361 drug recalls.

Did I read that correctly?

A. Yes.

Those are activities that the field does, staff of about 1,500 people. Yeah, this is the work that was actually completed. Yes.

Q. Okay. Let's go down to -- let's go down to Page 20, second paragraph, middle of the paragraph, but despite this commendable commitment of staff, we found that scientific capabilities and capacity at the FDA

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overall are unevenly meeting current requirements, have areas of serious deficiencies, and are not positioned to meet future needs. Most of these deficiencies are the result of the dramatic increase in responsibilities of the FDA on the one hand and the lack of increasing personnel and scientific expertise to fulfill these responsibilities on the other.

Did I read that correctly?

A. Yes.

Q. Okay. Next page.

Let's go down to Page 26, second-to-last paragraph, second-to-last sentence, the mission of getting safe and effective drugs to patients in a timely manner is currently threatened by inadequate expertise and capabilities.

A. Yes.

Q. Did I read that correctly?

A. Yes.

This is a paragraph describing the use of genetics and genome-wide association, which isn't really relevant to this product, but that's what this paragraph is about.

Q. Isn't it also referring to combination products?

A. Not products like Mirena. There are combinations of companion diagnostics where genomics is

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used to predict which cancers will respond to which drugs. So that's largely what they're referring to here.

Q. Let's go down to the bottom of that page. The area of drug safety now has several examples that favorably affect the benefit-risk ratio. Safety pharmacogenetics using genetic technologies can and have defined diagnostic profiles that can predict which patients should not risk an adverse event before they take the drug. The Subcommittee stressed the importance of safety science.

Did I read that correctly?

A. Yes.

They're giving an example of where the agency actually did this and resulted in a much safer use of a drug for HIV infection. There's another --

Q. Page 30, Section 3.1.3, there is insufficient capacity in modeling, risk assessment, and analysis. Recommendation: The FDA should immediately implement the IOM recommendations for improving drug safety as well as those made by the Subcommittee working group on bio -- on surveillance/biostatistics.

Did I read that correctly?

A. You did.

Q. Okay. Let's go to the next page, Page 31, first

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full sentence, we concur with the IOM's findings of scientific gaps in surveillance and biostatistics and are in substantial agreement with the IOM recommendations directed to the agency and with FDA's proposed response.

Did I read that correctly?

A. Yes.

This report is endorsing a request for agency to fund a program known as the Sentinel, the Sentinel System, which has been funded and is in place.

Q. Okay. Next paragraph, our findings and recommendations of the highest priority are summarized below. Although there are many needs, e.g., external collaborations and IT support, in all centers and programs, none of it -- none is as time sensitive and critical as surveillance and risk management.

Did I read that correctly?

A. Yes, you did.

Q. The Subcommittee found that there's an urgent need for developing and evaluating new statistical methods that are most appropriate for the data generated by new areas of science. The Subcommittee notes that new challenges are posed by the wealth of new types of data arising from animal studies, early clinical work, and new approaches to safety surveillance.

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Did I read that correctly?

A. Yes.

Q. Okay. Next paragraph down, second-to-the-last sentence, statistical and epidemiological expertise will need to be brought to bear on the most efficient and productive analytical approaches to identifying and evaluating signals arising from such databases.

A. Yes.

Q. Did I read that correctly?

A. Yes.

They're talking about microarray and system biology and genetic information databases.

Q. Yeah. I don't see that. It's actually --

A. Well, it's at the top.

Q. It's talking about the Center for Medicare and Medicaid and Veterans Administration databases, isn't it, sir?

A. Well, that relates to the Sentinel initiative. Yes, that's -- but it begins with methods to evaluate and appropriate data from microarray and systems biology experiments but then it does talk about the availability of -- this is the time period when we're starting to see electronic medical records and starting to utilize those, so this document was to help justify a request for FDA to set up a 100-million-patient database that

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FDA could do -- could access to actually use to help evaluate safety.
Q. The Subcommittee found that the FDA lacked sufficient expertise in quantitative methods, such as statistics and biomathematics, to effectively assess products and guide sponsors to design valid and informative studies.
Did I read that correctly?
A. You did.
I think it's referring back to the systems biology.
Q. Let's go to the next page. The Subcommittee found that the FDA also has a lack of expertise in risk/benefit assessment. The Subcommittee notes that another important area for quantitative methods development is risk/benefit assessment. Such assessments have traditionally been made informally but as the public's concern about the value and safety of new drugs continues to grow and as the complexity and volume of data informative about potential benefits and risks increases, more formal methods will be important for optimal decision-making.
Did I read that correctly?
A. Yes, you did.
Q. Okay. Going down, skipping that next

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recommendation in the interest of time, the Subcommittee recommends that the FDA strengthen the information tools for supporting effective risk management. This would provide the FDA with improved capacity to identify safety risks in advance and to conduct effective risk management, analysis, and communications. Key areas of focus would include providing improved database access and analysis and support of safety assessment, including access to health and public health databases for adverse event identification and the surveillance for risk identification and evaluation. It would also include the development of advanced data mining and analytical methodologies for signal detection in large health care databases.
Did I read that correctly?
A. Yes.
MR. SCHMIDT: Objection. You misread one word.
MR. JONES: That's okay.
THE WITNESS: But that does again refer to the FDA proposal to fund the Sentinel initiative.
MR. JONES: Okay.
BY MR. JONES:
Q. Let's go down to the bottom of Page 32. The FDA should also expand the drug safety framework to apply active surveillance to medical devices, animal drugs,

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and possibly foods as well as human drugs and biologics. This was at a minimum include providing access to existing databases with relevant medical information to FDA reviewers. It should increase the level of staff expertise in scientifically based risk communication strategies and increase the involvement of external stakeholders in the evaluation of FDA approaches and processes. The Subcommittee also urges the FDA to develop enhanced reviewer tools, such as data standards, electronic submissions, data mining and analysis as well as tools for electronic facilities, establishment, and product listing and tracking.
Did I read that correctly?
A. Yes.
And a lot of that has been done and even some of the methodologic work done by FDA statisticians on data mining are techniques that weren't used by either Dr. Ross or Dr. Etminan but which I've cited in my report.
MR. JONES: Okay. Strike as nonresponsive.
MR. SCHMIDT: Object to that motion.
BY MR. JONES:
Q. Page 34. Actually, let's go down to Page 42, Finding 3.2.2, Finding: The FDA has an inadequate and ineffective program for scientist performance. Recommendation: The FDA should enhance the program to

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monitor performance metrics and put the appropriate IT infrastructure in place to track the evolution of those metrics.
Did I read that correctly?
A. You did.
Q. Okay. Going down, the Subcommittee found that there needs to be more meaningful measures of scientific performance on the part of staff.
Then going to the last sentence, if performance is based on a noisy proxy, such as time to review a new product application, the pressure to perform can lead to unintended consequences, such as worse drug safety.
Did I read that correctly?
A. Yes.
That isn't what has happened but that -- you did read that.
Q. Okay. Finding 3.2.3. That's okay. We'll skip that in the interest of time.
MR. SCHMIDT: Because I think you are down to a few minutes. Ten minutes.
MR. JONES: Ten? Yeah, that's what I was thinking.
BY MR. JONES:
Q. Go to Page 47, Finding 3.3.2. Finding: The FDA lacks the information science capability and information

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infrastructure to fulfill its regulatory mandate.
Going down, the Subcommittee found that the FDA's current critical information supply chains are, at best, inefficient, cost intensive and prone to promote errors in regulatory science due to the inability to access, integrate, and analyze data. Incredibly, critical data resides in large warehouses sequestered in piles and piles of paper documents.
Did I read that correctly?
A. Yes.
I mean, it reflects the situation a decade ago but -- and not uniformly for FDA, but that certainly was true in 2007 for some parts of FDA.
MR. JONES: Move to strike as nonresponsive.
MR. SCHMIDT: Object to the motion.
BY MR. JONES:
Q. There are no effective mechanisms to protect these paper records, which include very valuable clinical trial data. Furthermore, processes for data and information exchange, both internally as well as among external partners, lack clear business processes, information technology standards, sufficient workforce expertise, a robust technology platform, such that FDA cannot credibly process, manage, protect, access, analyze, and leverage the vast amounts of data that it

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encounters. Consequently, the FDA's ability to support industry innovation and regulatory activities is compromised.
Did I read that correctly?
A. You did.
Q. Let's go to Page 48, second-to-last recommendation. The Subcommittee recommends that the FDA develop the capacity to do advanced data mining and use analytical methodologies and tool development for large databases as well as the development of new statistical methods and trial designs. This includes adverse event and signal detection, rapid portable diagnostic analytic testing, the development of risk-based models for selection of manufacturing inspections, risk communications science, and enhanced reviewer tools, such as data standards, electronic submissions, data mining analysis, and electronic product listing and tracking.
Did I read that correctly?
A. Yes. These are all things which are -- have been done since this report has been written.
Q. Let's go to Page 50, middle of the page. The Subcommittee found that in addition to deficiencies --
MR. SCHMIDT: Let him catch up.
THE WITNESS: Okay.

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BY MR. JONES:
Q. The Subcommittee found that in addition to deficiencies in its technology and communications platform, the FDA lacks many basic tools to support science and regulatory services. Specifically, the agency lacks the ability to adequately store data from clinical trials or adverse event reporting. The vast majority of these data are still paper based and sit in large warehouses, where it is not possible to efficiently access the data. The agency lacks adequate tools to search data, model the data, and analyze the data. FDA staff repeatedly emphasized the incredible missed opportunities that exist due to the inability to conduct safety and efficacy studies as a consequence of these deficiencies in storage, search, and core scientific tools.
Did I read that correctly?
A. You did.
I don't think the paragraph actually accurately describes the adverse reporting system, but you did read that correctly.
Q. Okay. When did you leave FDA?
A. In 2004.
Q. Okay. So that was three years before this report?

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A. Yes. And some of the things that they're describing in 2007 weren't accurate in 2004.
Q. Okay. So you disagree with the Committee.
A. I'm --
MR. SCHMIDT: Object to characterization.
THE WITNESS: Yes, I disagree with some of their conclusions and I think that some of their characterizations are overbroad and superficial.
This is a document that was prepared to support requests for funds in some of these areas and it was successful at doing this.
But, for example, with the adverse event reporting, I mean, you know since you've taken a look at AERS downloadable databases that those databases are updated quarterly, there's usually a few-month lag, and they've been provided and they were provided continuously all throughout this period and it existed in FDA databases, so they're -- this is a time when FDA is transitioning from paper to electronic records, and I think this report strongly supports that activity, which is now largely complete.
VIDEO OPERATOR: Source. Top right. Hit it twice, I think. One more time. Make sure the light is on the right.
MR. JONES: Yeah, here it is. Okay.

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BY MR. JONES:
Q. Dr. Feigal, do you remember participating in a discussion at -- with -- do you know what Eucomed is?
A. Yes. It's the medical device trade association in Europe.
Q. Okay. And do you remember giving an interview during your -- one of your interactions with that organization?
A. Yes. I don't remember the content, but I think you're going to help me remember what it was about.
Q. Okay.
MR. SCHMIDT: Can you just tell me what source you're about to play? Is this on the Internet? What is this?
MR. JONES: It's something that we got off of YouTube.
THE WITNESS: Oh.
MR. JONES: I'll cite the -- yeah. And you're famous.
THE WITNESS: Well, I've got a lecture I gave in San Diego that's on YouTube that --
MR. JONES: I've got that one too.
THE WITNESS: Yeah. Every time I see that, I conclude I needed a haircut before I gave that lecture.
MR. JONES: Okay. Let's watch this.

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MR. SCHMIDT: Can you just for the record cite the URL? I think that's what you were about to say.
MR. JONES: The sound is not working.
MR. SCHMIDT: While he's doing that, do you mind just telling us what the URL is?
MR. JONES: Christina, can you pull it?
MS. NATALE: Yeah.
VIDEO OPERATOR: I think it's because --
MS. NATALE: Because it's HDMI?
VIDEO OPERATOR: Yeah. If it's going to HDMI, we don't get the sound through here.
MR. JONES: You don't get the sound through the HDMI?
MS. NATALE: I'm trying. I'm sorry.
VIDEO OPERATOR: Do you want to go off the record real quick?
MR. JONES: Yeah, let's go off the record.
MR. SCHMIDT: I'm not going to agree to go off the record. We're almost done.
MR. JONES: Yeah, going -- we're going off the record.
MR. SCHMIDT: All right. Over my objection. We're counting this towards the time.
MS. NATALE: You have six minutes.
THE WITNESS: Off the record?

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MR. JONES: Yeah.
MR. SCHMIDT: I'm going to object to going off the record and request that we finish the deposition. There's five minutes left.
MR. JONES: It's my deposition. We're going off the record.
MR. SCHMIDT: Over my objection.
MR. JONES: That's okay.
VIDEO OPERATOR: Okay? Okay.
We're going off the record. The time is 6:01 p.m.
MR. SCHMIDT: Could we just go back on the record for five seconds so I can say on the record -- we can just do it on the stenography record.
From our perspective, the deposition is done in five minutes.
MR. JONES: We're off the record.
(Discussion off the record.)
VIDEO OPERATOR: We are back on the record. The time is 6:03 p.m.
BY MR. JONES:
Q. Dr. Feigal, so do you believe that FDA has adequate resources such that FDA always performs its job in accordance with its mission?
MR. SCHMIDT: Objection. Asked and answered.

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THE WITNESS: No. I think I have stated in, including in other testimony, that there are times that FDA needs to improve its resources and, in fact, I have -- when I was center director for Devices, I was an advocate for user fees to increase the resources of the Center and particularly pointed out resources needed for inspections. So there are areas where FDA resources are needed.
I think my points before may have related to the fact that the resources that are relevant for this trial or the resources in the review division and the reviewers have considered this product and I don't see anything in the record that suggests they didn't have the resources to do their job.
MR. JONES: Okay. Let's watch this video.
(Video played as follows:
"DR. FEIGAL: Well, I think they're becoming more similar but the biggest difference between the European and the U.S. is the utilization of third parties. In the U.S., the Food and Drug Administration has a tradition of doing its own inspection, its own reviews, and even to the extent that if they don't have enough resources to do all the inspections or to do all of the reviews, they leave them undone.")

BY MR. JONES:
Q. Is that you in the video?
A. It is.
Q. Do you remember saying that in that interview?
A. Yes. It's similar to something I said many times. We had a program in the Center for Devices where companies could opt to use third-party reviews and the program was underutilized. I was also an advocate for using third-party inspectors, the way that the Europeans do. So that's what this interview was about.
Q. Okay.
A. FDA doesn't have very many staff located outside the United States and so it's difficult for them to do the biannual manufacturing inspections outside the United States.
MR. JONES: I have no further questions for you, Dr. Feigal.
MR. SCHMIDT: Okay. Do you mind just reading into the record the URL?
MS. NATALE: I don't have it.
MR. JONES: Oh, here. I'll get it for you, Paul.
MR. SCHMIDT: Thank you. I appreciate it.
MR. JONES: The URL is HTTPS, hyphen, forward slash, forward slash, WWW dot YouTube dot-com, forward

slash, watch, question mark, V equals X, as in Xerox, L as in Larry, F as in Frank, 4, lower case A, H as in Harry, D as in David, L as in Larry, lower case TZY.
And just to clarify --
THE WITNESS: Of course.
MR. JONES: -- so everybody has it, the V is lower case V equals upper case XLF4, lower case A, upper case HDL, lower case TZ, upper case Y.
They don't make it easy.
MR. SCHMIDT: Here it is. Thank you.
THE WITNESS: You got it, huh? I'm impressed at your typing skills.
MR. SCHMIDT: That concludes the deposition.
MR. JONES: All right.
Thank you, Dr. Feigal.
THE WITNESS: You're welcome.
VIDEO OPERATOR: This concludes the deposition of David Feigal, consisting of four DVDs.
The time is 6:08 p.m.
We're off the record.
(Whereupon the deposition concluded at 6:08 p.m.)
TESTIMONY CLOSED

STATE OF CALIFORNIA)
COUNTY OF LOS ANGELES)
I, ROSEMARY LOCKLEAR, a Certified Shorthand Reporter of the State of California, duly authorized to administer oaths pursuant to Section 2025 of the California Code of Civil Procedure, do hereby certify that
DAVID WILLIAM FEIGAL, JR., M.D., M.P.H., the witness in the foregoing deposition, was by me duly sworn to testify the truth, the whole truth and nothing but the truth in the within-entitled cause; that said testimony of said witness was reported by me, a disinterested person, and was thereafter transcribed under my direction into typewriting and is a true and correct transcription of said proceedings.
I further certify that I am not of counsel or attorney for either or any of the parties in the foregoing deposition and caption named, nor in any way interested in the outcome of the cause named in said deposition dated the_____ day of _____, 2016.

ROSEMARY LOCKLEAR, RPR, CRR, CSR 13969

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the Errata Sheet for any corrections that are made.
After doing so, please sign the Errata Sheet and date it.
You are signing same subject to the changes you have noted on the Errata Sheet, which will be attached to your deposition.
It is imperative that you return the original Errata Sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

E R R A T A

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ACKNOWLEDGEMENT OF DEPONENT

I, _____, do hereby certify that I have read the foregoing pages, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

_____

DAVID WILLIAM FEIGAL, JR., M.D., M.P.H. DATE

Subscribed and sworn
to before me this
_____ day of _____, 20____.

My commission expires:_____

_____

Notary Public

LAWYER'S NOTES

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